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NEW SYNTHESES OF 2-ALKYLTHIO-4-OXO-3,4-DIHYDRO-QUINAZOLINES, 2-ALKYLTHIOQUINAZOLINES, AS WELL AS THEIR HETERO ANALOGUES

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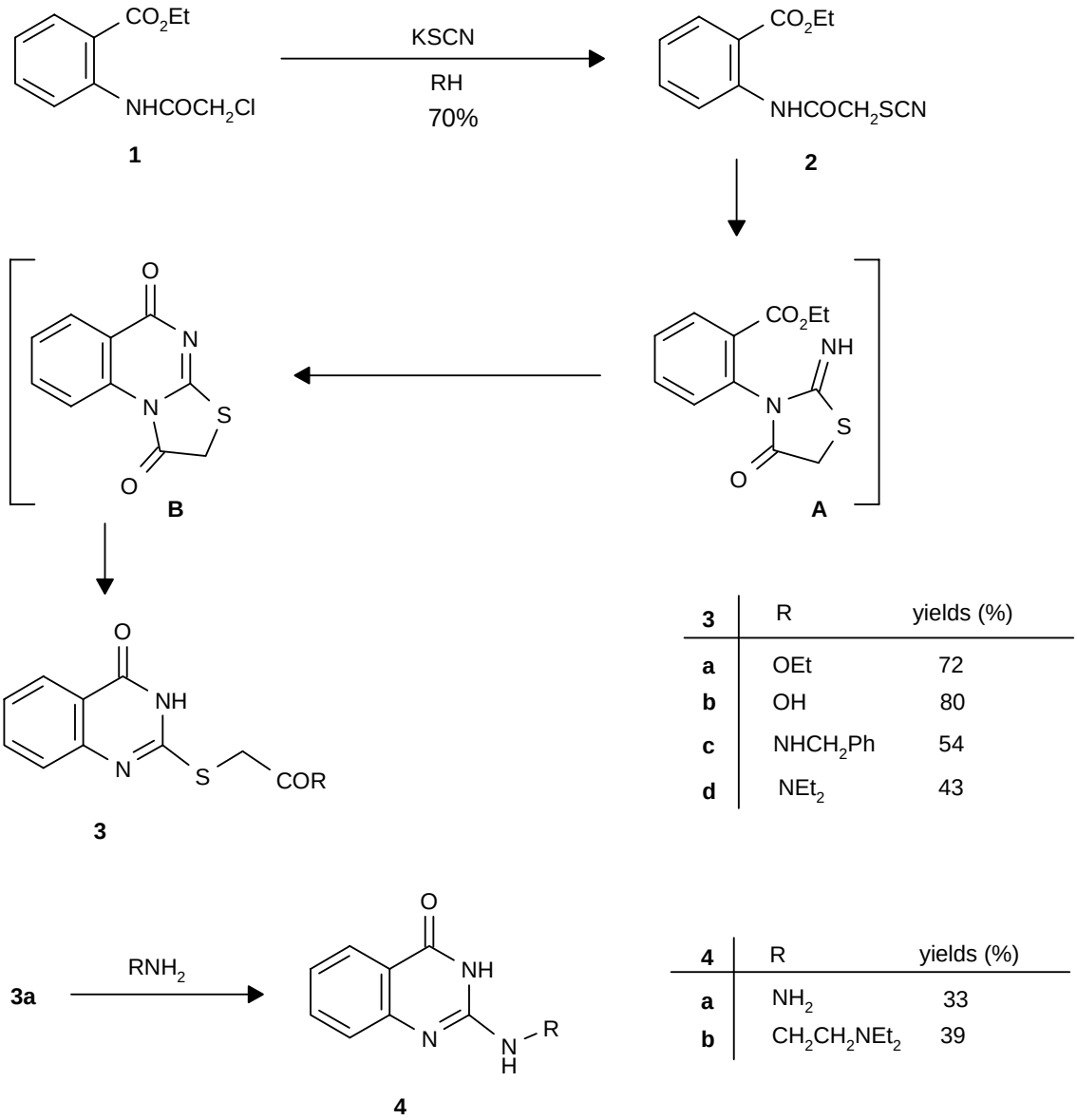
Abstract - *N*-Chloroacetylanthranilic acid ethyl ester reacts with potassium thiocyanate in the presence of alcohol to give the (4-oxo-3,4-dihydroquinazolin-2-yl-sulfanyl)acetic acid ester (**3a**). In the presence of water or amines the acetic acid derivative (**3b**) or the acetamide derivatives (**3c,d**) are obtained. 2-Amino-4-oxo-3,4-dihydroquinazolines (**4**) arise if vigorous reaction conditions are employed. Analogously, *N*-chloroacetyl derivatives of 5-membered heterocycles with enaminocarbonyl structure (**5**, **7**, **9**, **11**, **13**, **20**, **23**) react with potassium thiocyanate to yield thieno[2,3-*d*]-, thieno[3,2-*d*]-, imidazo[4,5-*d*]-, pyrrolo[3,2-*d*]-, and thiazolo[4,5-*d*]pyrimidines (**6**, **8**, **10**, **12**, **14**, **21**, **24**). Quinazolines (**18**, **19**) are formed from the reaction of 2-chloroacetylaminoacetophenone (**16a**) and 2-chloroacetylaminobenzophenone (**16b**) with potassium thiocyanate and subsequent treatment of the intermediates with amines.

In our investigations about the synthesis of quinolines and quinazolines from *N*-chloroacetylanthranilic acid derivatives, we continued our experimental work in order to examine the synthetic potentials of *N*-chloroacetylanthranilic acid ethyl esters and hetero analogues in reactions with potassium thiocyanate under various reaction conditions. In earlier publications we demonstrated that the ring closure reactions starting from *N*-chloroacetylanthranilic acid derivatives give access to a multitude of different substitution patterns, if the chloro atom is substituted by an aminoalkyl [1] or preferably an electron withdrawing group such as cyano, pyridinio,[2] or sulfonio.[3] Thieno[2,3-*d*]pyrimidines were reported to furnish various pharmacological activities.[4] With the described reaction here a new access opened up to the 2-alkylthio-quinazolines and their hetero analogues.

RESULTS AND DISCUSSION

N-Chloroacetylanthranilic acid ethyl ester (**1**) was expected to yield a quinoline derivative after substitution of the chloro atom by the thiocyanato group and subsequent ring closure reaction by Dieckmann condensation under alkaline conditions. On heating of a suspension of *N*-chloroacetyl-anthranilic acid ethyl ester (**1**) and potassium thiocyanate in acetonitrile the primary substitution product 2-thiocyanato-acetylaminobenzoic acid ethyl ester was obtained. In case that an alcohol was used as a solvent the reaction proceeded further to furnish a 4-oxo-3,4-dihydroquinazoline derivative (**3**).



1 **2** **A** **B** **3** **3a** **4**

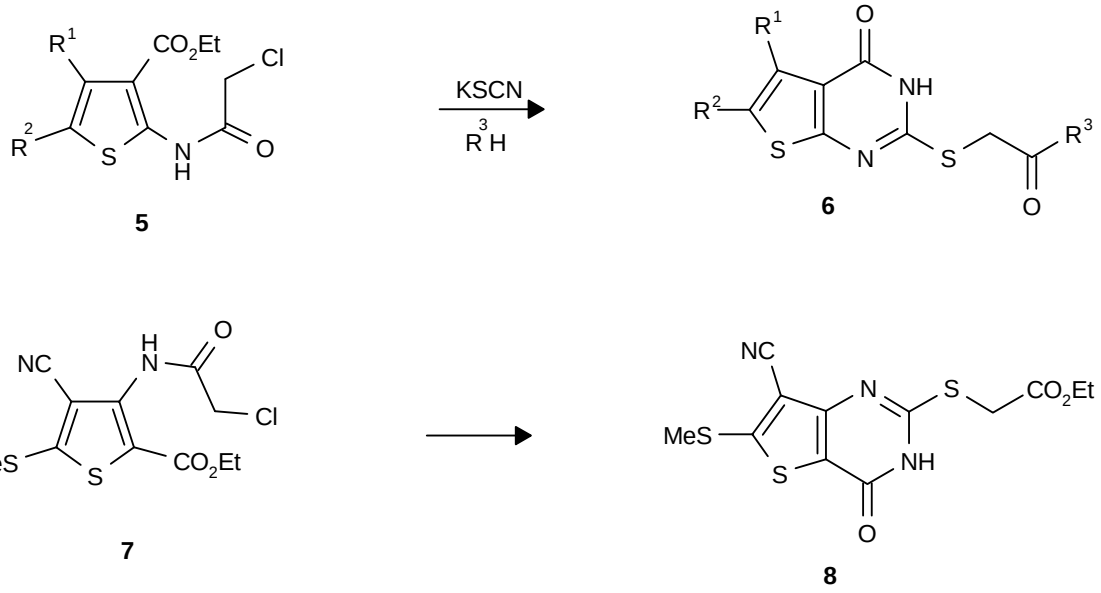
3	R	yields (%)
a	OEt	72
b	OH	80
c	$NHCH_2Ph$	54
d	NEt_2	43

4	R	yields (%)
a	NH_2	33
b	$CH_2CH_2NEt_2$	39

Scheme 1

As described in an earlier publication,[5] we observed the same course of reaction with 2-chloroacetyl-aminobenzonitrile, which gave rise to 4-aminoquinazoline derivative on reaction with potassium thiocyanate in the presence of alcohol. The indicated intermediates cannot be isolated, but can be

rationalized as follows (Scheme 1). The 2-iminothiazolidin-4-one intermediate was found to be isolable in the reaction of 2-chloroacetylaminoacetophenone with potassium thiocyanate. The subsequent intermediate representing a thiazolo [3,2-*a*] quinazoline system is a probable structure because experiments failed to open the 2-imino-3-phenylthiazolidin-4-one ring, which was prepared from chloroacetanilide and potassium thiocyanate, by treatment with alcohol. An similar but mesoionic isolable thiazole structure was reported to arise from the reaction of 2-thioxo-4-oxoquinazolines with acetic anhydride in the presence of pyridine.[6]



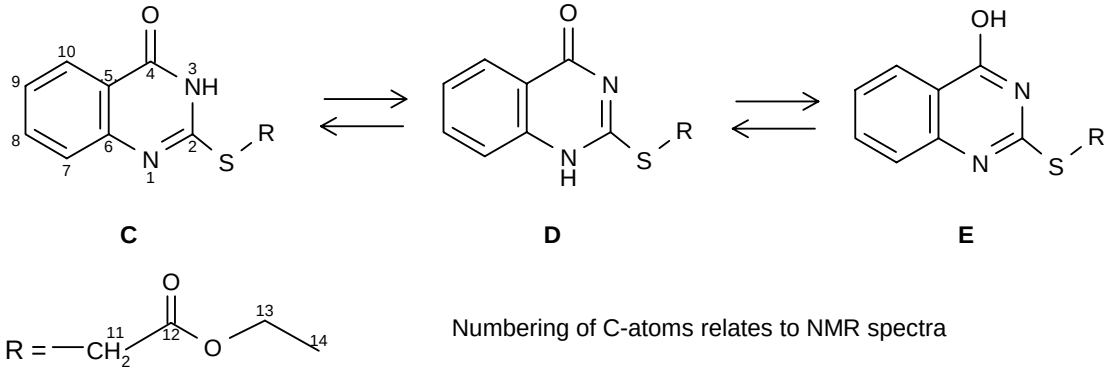
5,6	R^1	R^2	R^3	yields (%) of **6**
a	Me	Me	OEt	34
b	Me	CO_2Et	OEt	40
c		- $(CH_2)_4$ -	OEt	51
d	Me	Me	OH	28
e	Me	Me	$N(CH_2CH_2)_2O$	41

Scheme 2

An earlier described synthesis of (4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetic acid derivatives were employed the alkylation of 2-mercapto-4-oxoquinazolines with haloacetic acid derivatives.[7-10]

Compound (**3a)** was earlier described [9,10] without indication of the preferred tautomeric structure in solution. One would have to differentiate between three lactam-lactim tautomers, which must be taken in consideration (*see* Figure 1). We were able to prove by 2D-NMR spectroscopy that structure (**C**) is existent in DMSO-d_6 solution. From the NOESY spectrum as well as from $^1H/^{13}C$ correlated HSQC and HMBC spectra an assignment of the ^1H- and ^{13}C-NMR signals was accomplished, whereby on account of

the rapid proton exchange it was not possible to decide unambiguously in favour of one of the tautomers (**C**) or (**E**).



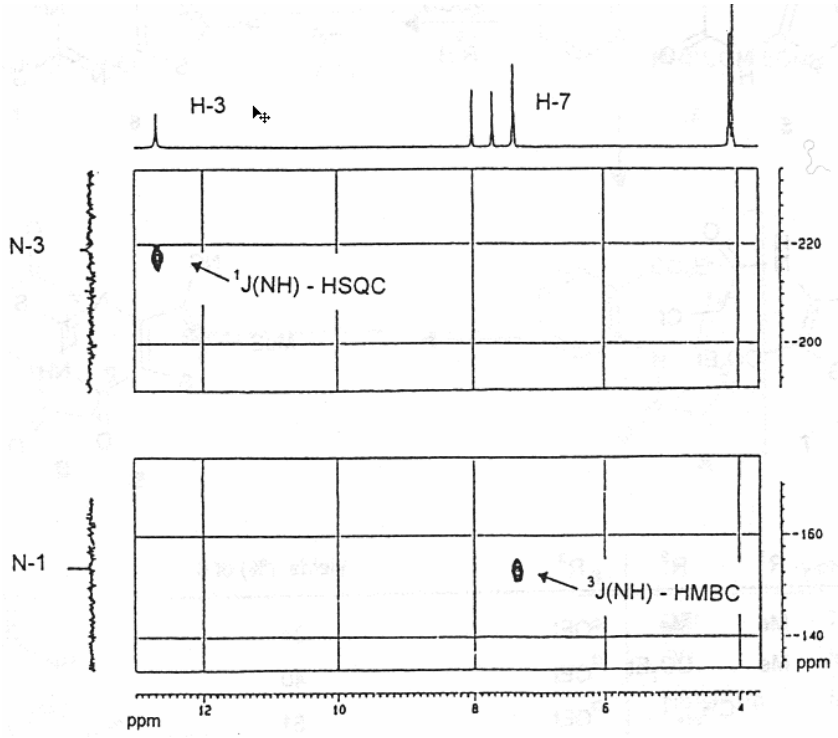
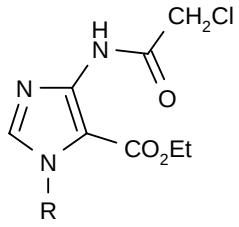


Figure 1 2D - $^{1}H/^{15}N$-HSQC and $^{1}H/^{15}N$-HMBC-NMR spectra of **3a** in DMSO-d_6

A decision in favor of structure (**C**) was possible, because the ^{15}N-NMR-spectrum of **3a** exhibits two signals at -219.1 ppm and -153.8 ppm (reference to $\delta(^{15}N)$ CH_3NO_2 = 0 ppm), which we correlated in the $^{1}H/^{15}N$-correlated HSQC and HMBC spectra to the proton signals at 12.69 ppm (^{1}J, H-3/N-3) and 7.41 ppm (^{3}J, H-7/N-3) respectively (*see* Figure 1).

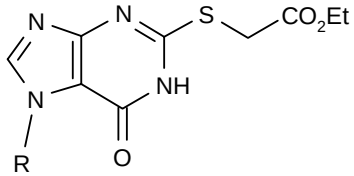
N-Chloroacetylanthranilic acid ethyl ester (**1**) reacts also in a solvent mixture of acetonitrile and water to give 2-thiocyanatoacetylaminobenzoic acid ethyl ester, but this intermediate is directly converted to the (4-oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetic acid (**3b**). When primary or secondary amines are used instead of alcohol in the reaction with 2-thiocyanatoacetyl-aminobenzoic acid ethyl ester (**2**) or the

precursor *N*-chloroacetyl anthranilic acid ethyl ester /potassium thiocyanate, the (4-oxo-3,4-dihydro-quinazolin-2-ylsulfanyl)acetic acid amides (**3c** and **d**) are formed.



9

KSCN, EtOH



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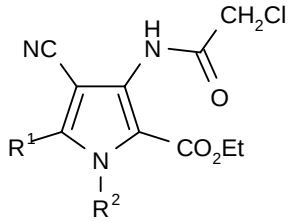

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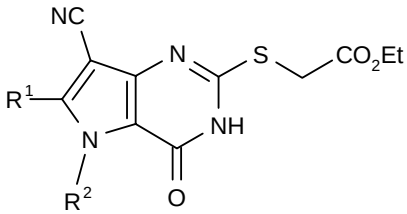
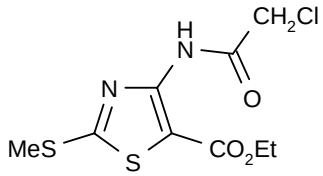
KSCN, EtOH



12

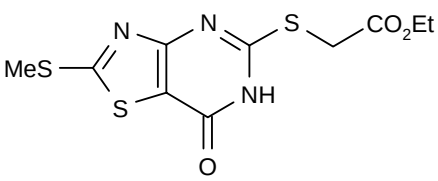
9,10	R	Yields (%)
a	*p*-Cl-C_6H_4	42
b	*p*-MeO-C_6H_4	79

11,12	R^1	R^2	Yields (%)
a	H	*p*-MeO-C_6H_4	65
b	MeS	H	55



13

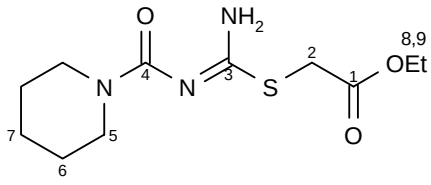
73% KSCN, EtOH



14

piperidine

55%



15

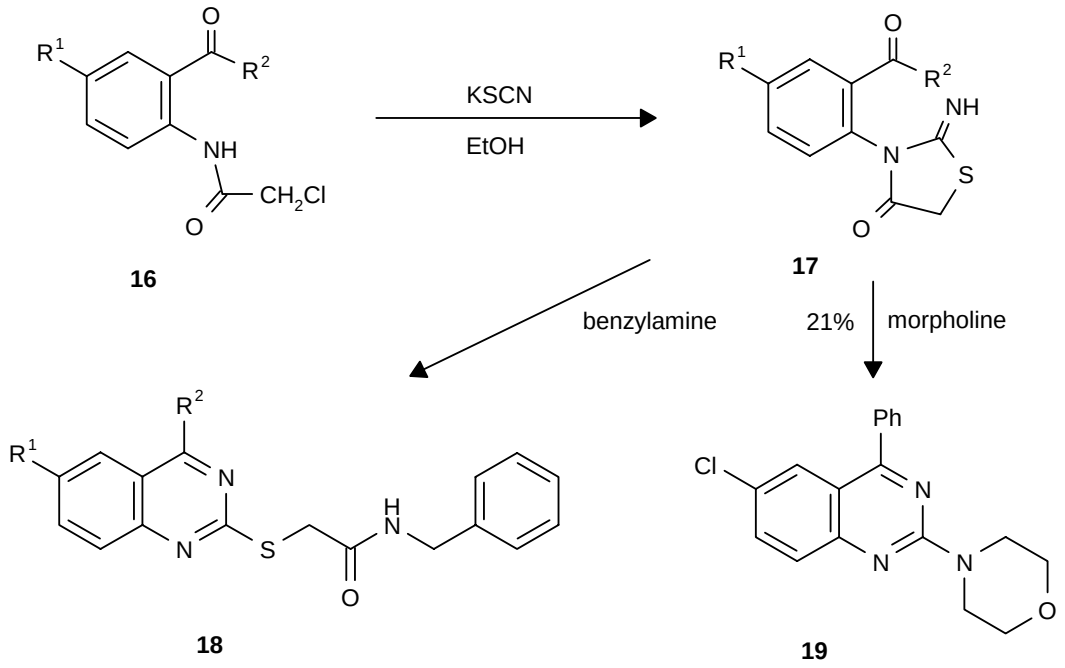
Numbering of C-atoms relates to NMR spectra

Scheme 3

Treatment of **3a** with primary amines leads to the formation of 2-amino-4-oxo-3,4-dihydro-quinazolines (**4a** and **b**) under elimination of the thioacetic acid moiety.

Further investigations involved *N*-chloroacetyl derivatives of 5-membered heterocycles with enamino-carbonyl structure. The employed 5-membered heterocycles were synthesized according to well-known literature procedures.[11-14] The syntheses of *N*-chloroacetyl derivatives were carried out following ageneral applicable method as described by Sauter.[15]

The utilization of the method for the synthesis of various hetero-condensed pyrimidin-4-ones starting from *N*-chloroacetylated amino-heterocycles was examined. Analogously, *N*-chloroacetyl derivatives of 5-membered amino-heterocycles with carboxylic acid ester groups gave the same reaction with potassium thiocyanate and alcohol as observed with *N*-chloroacetylanthranilic acid ethyl ester (**1**). Schemes 2 and 3 illustrate the structure of respective starting materials (**5**, **7**, **9**, **11**, and **13**) and products (**6**, **8**, **10**, **12**, and **14**).



16 **17** **18** **19**

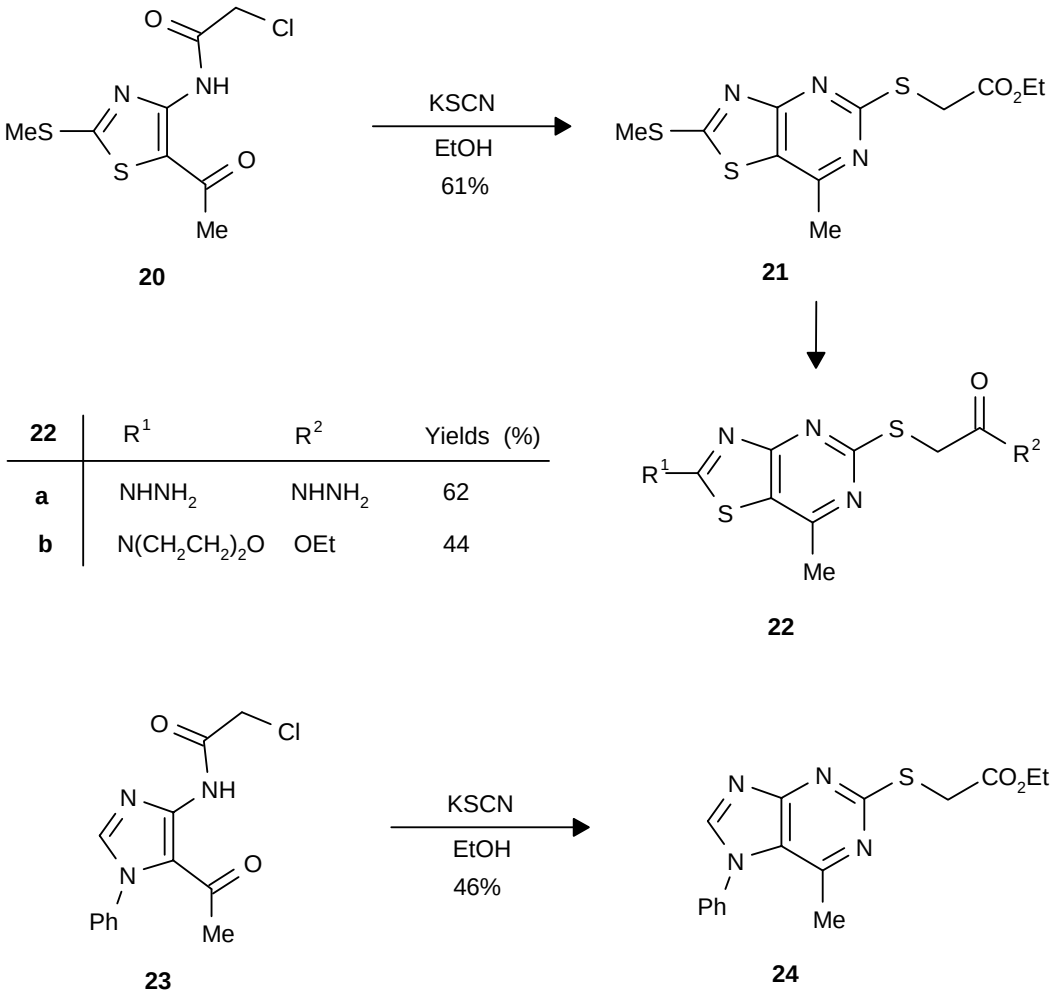
16 - 18	R^1	R^2	Yields (%) of **17**	Yields (%) of **18**
a	H	Me	43	25
b	Cl	Ph	33	40

Scheme 4

The thiazolo[4,5-*d*]pyrimidine (**14**) proved to be exceptionally unstable on treatment with piperidine as an amine for further derivatization, and at this, complete cleavage of the condensed heterocyclic system was observed.

For further investigations (*see* Schemes 4 and 5) we extended our synthetic method to 2-chloro-acetyl-aminoacetophenone (**16a**) and 2-chloroacetylamino-4-chlorobenzophenone (**16b**) and obtained as primary

reaction product with potassium thiocyanate the anticipated 2-iminothiazolidin-4-one intermediates (**17**). A conversion of **17** with amines yield either (quinazolin-2-ylsulfanyl)acetamides (**18**) or 2-aminoquinazolines (**19**) depending obviously on the nucleophilicity of the amine. Ketones of 5-membered aminoheterocylces were also included in the investigation of pyrimidine ring formation. *N*-chloroacetylaminothiazole (**20**) yields the thiazolo[4,5-*d*]pyrimidine (**21**), which was further derivatized with amines to amino-substituted compounds (**22**), and *N*-chloroacetylaminoimidazole (**23**) gives the respective imidazo[4,5-*d*]pyrimidine derivative (**24**).



20 **21** **22** **23** **24**

22	R^1	R^2	Yields (%)
a	$NHNH_2$	$NHNH_2$	62
b	$N(CH_2CH_2)_2O$	OEt	44

Scheme 5

The yields were not optimized. Therefore nothing can be said about possible side reactions.

ACKNOWLEDGEMENT

The authors are indebted to Mrs. Pinske for microanalyses.

EXPERIMENTAL

The corrected melting points were measured on a Kofler hot-stage apparatus. ^{1}H-, ^{13}C-, and ^{15}N-NMR spectra and 2D-NMR spectra were obtained in DMSO-d_6 using the Bruker AC-200 MHz and DRX-500 MHz spectrometers. ^{1}H- and ^{13}C-chemical shifts are reported in ppm downfield from TMS as a internal standard. The ^{15}N-chemical shifts are downfield positive to $CH_3{}^{15}NO_2$ = 0 ppm as a external standard.

The IR spectra were recorded on a spectrophotometer Specord 75 (Fa. Carl-Zeiss Jena). Elemental analyses were determined on an EA 1108 (Fa. Carlo Erba Hofheim). The MS spectra were obtained by the HP-Bruker Esquire-LC-MS System.

Chloroacetylation - general procedure [15]

10 mmol of amino-substituted heterocyclic compound or amino-substituted benzene derivative are suspended in dioxane (10 mL). Chloroacetyl chloride (1.36 g, 12 mmol) are added dropwise to the stirred suspension within 30 min. After stirring for additional 2 h, the reaction mixture is poured into water (100 mL), the precipitate collected by filtration, and the crude product recrystallized from ethanol.

2-Thiocyanatoacetylaminobenzoic acid ethyl ester (**2**)

A suspension of **1** (2.42 g, 10 mmol) and potassium thiocyanate (3.0 g, 30 mmol) in MeCN (50 mL) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (150 mL) and after 1 h, the crude product was collected by filtration. Yield: 1.85 g (70 %), mp 62-63 °C (EtOH); IR (KBr): 2150 (SCN), 1695 (CO), 1670, 1580 (CO, secondary amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 10.92 (1H, s, NH), 7.11-8.08 (4H, m, benzo-H), 4.20 (2H, q, J =6.95 Hz, OCH_2 and 2H, s, SCH_2), 1.22 (3H, t, J =6.95 Hz, CH_3); EI-MS *m/z* : 264 (M^+). *Anal.* Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.6; S, 12.13. Found: C, 54.82 ; H, 5.01; N, 11.02; S, 11.93.

(4-Oxo-3,4-dihydroquinazolin-2-ylsulfanyl)acetic acid ethyl ester (**3a**)

A suspension of **1** (2.42 g, 10 mmol) and potassium thiocyanate (3.0 g, 30 mmol) in EtOH (50 mL) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (150 mL) and after 1 h, the crude product was collected by filtration. Yield: 2.1 g (72 %), mp 179-180 °C (MeOH), lit.[2], mp 186-187 °C (EtOH); IR (KBr): 3450 (br, NH), 1692, 1734 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 12.69 (1H, br s, NH), 7.40-8.10 (4H, m, benzo-H), 4.13 (2H, q, J =7.15 Hz, OCH_2), 4.07 (2H, s, SCH_2), 1.19 (3H, t, J =7.14 Hz, CH_3); ^{13}C-NMR (DMSO-d_6) δ : 14.16 (CH_3, C-14), 32.46 (SCH_2, C-11), 61.17 (OCH_2, C-13), 119.97 (C-5), 125.80 (CH=, C-9), 125.92 (CH=, C-7), 126.12 (CH=, C-10), 134.68 (CH=, C-8), 148.22 (C-6), 154.76 (C-2), 161.15 (C-4), 168.32 (C-12); ^{15}N-NMR (DMSO-d_6) δ : -153.8 (N-1), -219.1 (NH, N-3). El-MS *m/z* : 265 (M^+).

(4-Oxo-3,4-dihydroquinazolin-2-ylsulfanyl) acetic acid (3b)

A suspension of **1** (2.42 g, 10 mmol) and potassium thiocyanate (3.0 g, 30 mmol) in a mixture of aceto-

nitrile (50 mL) and water (20 mL) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (100 mL) and after 1 h, the crude product was collected by filtration. Yield: 1.9g (80 %), mp 220-222 °C (1,4-dioxane); ^{1}H-NMR (DMSO-d_6) δ : 12.82 (2H, br s, OH, NH), 7.11-8.10 (4H, m, benzo-H), 4.05 (2H, s, SCH_2); *Anal.* Calcd for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41; N, 11.86; S, 13.57. Found: C, 51.12; H, 3.61; N, 11.74; S, 13.18.

(4-Oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-*N*-benzylacetamide (**3c**)

A suspension of **1** (4.84 g, 20 mmol) and potassium thiocyanate (6.0 g, 60 mmol) in EtOH (60 mL) and benzylamine (4 mL, 40 mmol) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (200 mL) and after 1 h, the precipitate was collected by filtration and washed with water. Yield: 3.5 g (54 %), mp 205-208°C (decomp) (AcOH); IR (KBr): 3288 (br, NH), 1672, 1588 (CO, secondary amide) cm^{-1}, ^{1}H-NMR (DMSO-d_6) δ : 12.31 (1H, s, NH), 8.68 (1H, t, J =5.7 Hz, NH), 7.11-8.03 (9H, m, phenyl-H, benzo-H), 4.21 (2H, d, J =5.7 Hz, NCH_2), 4.03 (2H, s, SCH_2); *Anal.* Calcd for $C_{17}H_{15}N_3O_2S$: C, 62.75; H, 4.65; N, 12.91; S, 9.85. Found: C, 62.93; H, 4.75; N, 13.09; S, 9.77.

(4-Oxo-3,4-dihydroquinazolin-2-ylsulfanyl)-*N*,*N*-diethylacetamide (**3d**)

A suspension of **2** (5.28 g, 20 mmol) and some crystals of potassium thiocyanate in diethylamine (50 mL) was heated to reflux for 3 h. The reaction mixture was cooled and poured into water (200 mL) and after acidification with hydrochloric acid, a yellow precipitate was collected by filtration and washed with water. Yield: 2.5 g (43 %), mp 143-147 °C (decomp) (EtOH); IR (KBr): 3430 (br, NH), 1698 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 12.73 (1H, s, NH), 7.50-8.01 (4H, m, benzo-H), 4.19 (2H, s, SCH_2), 3.52 (4H, m, $2NCH_2$), 1.02 and 1.09 (6H, each t, J =7.15 Hz, $2\times CH_3$) ; *Anal.* Calcd for $C_{14}H_{17}N_3O_2S$: C, 57.71; H, 5.88; N, 14.42; S, 11.00. Found: C, 57.94; H, 5.47; N, 13.56; S, 11.01.

2-Hydrazino-4-oxo-3*H*-quinazoline (**4a**)

A suspension of **3a** (1.32 g, 5 mmol) in a mixture of EtOH (15 mL) and hydrazine hydrate (5 mL, 80 %, 80 mmol) is stirred at 20ºC for 2 h and then allowed to react completely over a period of 2 d. Subsequently, the solution is filtrated and diluted with water (5 mL) and the precipitate separated by filtration. The filtrate is concentrated by evaporation, the formed precipitate separated again and combined with the first crop. Yield: 0.29 g (33 %), mp 355 °C(decomp), lit.,[5]: mp 360 °C(decomp); IR (KBr): 3305, 3190 (NH) cm^{-1}; *Anal.* Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.63; H, 4.62; N, 32.12.

2-Diethylaminoethylamino-4-oxo-3*H*-quinazoline (**4b**)

A suspension of **3a** (6.34 g, 24 mmol) and ammonium chloride (0.1 g, 2 mmol) indiethylaminoethylamine (7 mL, 50 mmol) is stirred and the temperature slowly elevated up to 120 °C. After start of evolution of methyl mercaptan, the mixture is heated to boiling for 30 min in order to complete the reaction. After cooling of the mixture, warm EtOH (10 mL) is added and then the reaction mixture is poured into water

(150 mL) and the precipitate separated by filtration. Yield: 2.6 g (39 %), mp 72-75 °C (EtOH/H_2O=1:1); IR (KBr): 3400, 3230 (NH) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 7.13-7.89 (4H, m, benzo-H), 6.31 (1H, s, NH), 3.38 (4H, m, 2×NCH_2), 2.50 (4H, m, 2×NCH_2), 1.03 (6H, t, *J* =7.10 Hz, 2×CH_3) ; *Anal.* Calcd for $C_{14}H_{22}N_4O_2$: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.25; H, 8.32; N, 19.86.

(6,7-Dimethyl-1-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidin-3-ylsulfanyl)acetic acid ethyl ester (**6a**)

A suspension of **5a** (2.76 g, 10 mmol, prepared from 2-amino-4,5-dimethyl-3-thiophenecarboxylic acid ethyl ester by chloroacetylation according to the general method [15]) and potassium thiocyanate (3.0 g, 30 mmol) in abs. EtOH (50 mL) is stirred and heated to reflux for 3 h. After cooling the mixture is poured into water (50 mL), the precipitate is allowed to settle for 12 h and then separated by filtration. Yield: 1.0 g (34 %), mp 174-175 °C ($MeNO_2$); ^{1}H-NMR (DMSO-d_6) δ : 12.72 (1H, br s, NH), 4.13 (2H, q, *J* = 6.90 Hz, OCH_2), 4.00 (2H, s, SCH_2), 2.32 (6H, s, $2CH_3$), 1.18 (3H, t, *J* =6.90 Hz, CH_3); EI-MS *m/z* : 299 (M^+). *Anal.* Calcd for $C_{12}H_{14}N_2O_3S_2$: C, 48.30; H, 4.73; N, 9.39; S, 21.49. Found: C, 47.93; H, 4.44; N, 9.52; S, 21.22.

(6-Carbethoxycarbonyl-7-methyl-1-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidin-3-ylsulfanyl)acetic acid ethyl ester (**6b**)

As described in the procedure for **6a**, compound **(6b)** is obtained from **5b** (3.34 g, 10 mmol, prepared from 2-amino-4-methyl-3,5-thiophenedicarboxylic acid diethyl ester by chloroacetylation according to the general method).[15] Yield: 1.41 g (40 %), mp 174-176 °C (EtOH); *Anal.* Calcd for $C_{14}H_{16}N_2O_5S_2$: C, 47.18; H, 4.52; N, 7.86; S, 17.99. Found: C, 47.32; H, 4.71; N, 7.65; S, 17.81.

(6,7-Tetramethylene-1-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidin-3-ylsulfanyl)acetic acid ethyl ester (**6c**)

As described in the procedure for **6a**, compound **(6c)** is obtained from **5c** (3.02 g, 10 mmol, prepared from 2-amino-4,5-tetramethylene-3-thiophenecarboxylic acid ethyl ester by chloroacetylation according to the general method).[15] Yield: 1.65 g (51 %), mp 183-185 °C ($MeNO_2$); *Anal.* Calcd for $C_{14}H_{16}N_2O_3S_2$: C, 51.83; H, 4.97; N, 8.63; S, 19.77. Found: C, 51.38; H, 5.01; N, 8.37; S, 19.76.

6,7-Dimethyl-1-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidin-3-ylsulfanyl)acetic acid (**6d**)

A suspension of **5a** (5.52 g, 20 mmol, prepared from 2-amino-4,5-dimethyl-3-thiophenecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (6.0 g, 60 mmol) in acetonitrile (60 mL) is heated to reflux for 1 h. Subsequently, dimethylaminoethanol (3 mL, 30 mmol) is added and the mixture heated to reflux for additional 1 h. After cooling the reaction mixture is poured into water (300 mL) and neutralized by addition of 5% hydrochloric acid. The precipitate is separated by filtration. Yield: 1.52 g (28 %), mp 211-215 °C (DMF); IR (KBr): 3400 (NH), 1679 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 12.60 (2H, s, OH, NH), 4.00 (2H, s, SCH_2), 2.28 (6H, s, 2×CH_3) ; *Anal.*

Calcd for $C_{10}H_{10}N_2O_3S_2$: C, 44.43; H, 3.73; N, 10.36; S, 23.72. Found: C, 45.02; H, 4.04; N, 10.40; S, 23.45.

6,7-Dimethyl-1-oxo-1,2-dihydrothieno[2,3-*d*]pyrimidin-3-ylsulfanyl)acetic acid morpholide (**6e**)

A suspension of **5a** (5.52 g, 20 mmol, prepared from 2-amino-4,5-dimethyl-3-thiophenecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (6.0 g, 60 mmol) in a mixture of abs. EtOH (100 mL) and morpholine (2 mL, 23 mmol) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (300 mL), the precipitate is separated by filtration and washed with water. Yield: 2.80 g (41 %), mp 166-169 °C ($MeNO_2$); IR (KBr): 3300-3400 (br s, NH), 1650 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 12.78 (1H, s, NH), 4.08 (2H, s, SCH_2), 3.50 (8H, m, $2NCH_2$, $2OCH_2$), 2.23 (6H, s, $2\times CH_3$); *Anal.* Calcd for $C_{14}H_{17}N_3O_3S_2$: C, 49.54; H, 5.05; N, 12.38; S, 18.89. Found: C, 49.31; H, 5.03; N, 12.56; S, 19.23.

7-Cyano-6-methylthio-4-oxo-3,4-dihydrothieno[3,2-*d*]pyrimidin-2-ylsulfanyl)acetic acid ethyl ester (**8**)

A suspension of **7** (3.19 g, 10 mmol, prepared from 2-amino-4-cyano-5-methylthio-2thiophenecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (3.0 g, 30 mmol) in abs. EtOH (60 mL) is heated to reflux for 2 h. After cooling the reaction mixture is poured into water (300 mL), the precipitate is separated by filtration and washed with water. Yield: 2.90 g (85 %), mp 169-171 °C (abs. EtOH); IR (KBr): 3315 (OH), 2229 (CN), 1734 (CO) cm^1; ^{1}HNMR (DMSO-d_6) δ : 9.58 (1H, s, NH), 4.33 and 4.39 (2H, AB, SCH_2), 4.27 (2H, q, J =7.10 Hz, OCH_2), 2.91 (3H, s, CH_3), 1.3 (3H, t, J =7.10 Hz, CH_3); EI-MS *m/z* : 341 (M^+), *Anal.* Calcd for $C_{12}H_{11}N_3O_3S_3$: C, 42.21; H, 3.25; N, 12.31; S, 28.17. Found: C, 42.51; H, 3.61; N, 11.98; S, 28.05.

[1-(4-Chlorophenyl)-7-oxo-6,7-dihydroimidazo[4,5-*d*]pyrimidin-5-ylsulfanyl]acetic acid ethyl ester (**10a**)

A suspension of **9a** (4.45 g, 13 mmol, prepared from 4-amino-1-(4-chlorphenyl)-1*H*-5-imidazolecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15]and potassium thiocyanate (3.9 g, 40 mmol) in abs. EtOH (60 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (200 mL), the precipitate is separated by filtration and washed with water. Yield: 2.0 g (42 %), mp 200-204 °C (decomp)(EtOH)); IR (KBr): 3430, 3170 (NH), 1700 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 11.61 (1H, s, NH), 8.00 (1H, s, CH), 7.45-7.57 (4H, AA`XX`, J =8.1 Hz, phenyl-H), 4.04 (2H, q, J =7.0 Hz, OCH_2), 3.95 (2H, s, SCH_2), 1.05 (3H, t, J =7.0 Hz, CH_3); *Anal.* Calcd for $C_{15}H_{13}N_4O_3ClS$: C, 49.38; H, 3.59; N, 15.36; Cl, 9.72; S, 8.79. Found: C, 49.42; H, 3.63; N, 15.21; Cl, 9.86; S, 8.25.

[1-(4-Methoxyphenyl)-7-oxo-6,7-dihydroimidazo[4,5-*d*]pyrimidin-5-ylsulfanyl]acetic acid ethyl ester (**10b**)

A suspension of **9b** (6.76 g, 20 mmol, prepared from 4-amino-1-(4-methoxyphenyl)-1*H*-5-imidazole-carboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (6.0 g, 60 mmol) in abs. EtOH (100 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (200 mL), the precipitate is separated by filtration and washed with water. Yield: 5.36 g (74 %), mp 198-200 °C (EtOH)); IR (KBr): 3450 (NH), 1715 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 11.78 (1H, s, NH), 7.91 (1H, s, CH), 7.01-7.31 (4H, AA`XX`, *J* =8.25 Hz, phenyl-H), 4.02 (2H, q, *J* =7.0 Hz, OCH_2), 3.93 (2H, s, SCH_2), 3.35 (3H, s, OCH_3), 1.05 (3H, t, *J* =7.0 Hz, CH_3); *Anal.* Calcd for $C_{16}H_{16}N_4O_4S$: C, 53.32; H, 4.47; N, 15.55; S, 8.89. Found: C, 53.66; H, 4.54; N, 15.49; S, 8.42.

[7-Cyano-5-(4-methoxyphenyl)-4-oxo-3,4-dihydropyrrolo[3,2-*d*]pyrimidin-2-ylsulfanyl]acetic acid ethyl ester (**12a**)

A suspension of **11a** (4.34 g, 12 mmol, prepared from 3-amino-4-cyano-1-(4-methoxyphenyl)-1*H*-2-pyrrolecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (3.6 g, 37mmol) in abs. EtOH (120 mL) is heated to reflux for 5 h. After cooling the reaction mixture is poured into water (300 mL), the precipitate is separated by filtration and washed with water. Yield: 3.0 g (65 %), mp 183-186 °C (EtOH) ; IR (KBr): 3450 (NH), 2233 (CN), 1731 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 9.50 (1H, s, NH), 8.21 (1H, s, CH), 7.05 and 7.38 (4H, AA`XX`, *J* =8.25 Hz, phenyl-H), 4.28 (2H, q, *J* =7.1 Hz, OCH_2), 4.01 (2H, s, SCH_2), 3.85 (3H, s, OCH_3), 1.07 (3H, t, *J* =7.1 Hz, CH_3); *Anal.* Calcd for $C_{18}H_{16}N_4O_4S$: C, 56.24; H, 4.65; N, 14.57; S, 8.34. Found: C, 56.41; H, 4.84; N, 14.55; S, 8.36.

(7-Cyano-6-methylthio-4-oxo-3,4-dihydropyrrolo[3,2-*d*]pyrimidin-2-ylsulfanyl)acetic acid ethyl ester (**12b**)

A suspension of **11b** (4.53 g, 15 mmol, 3-amino-4-cyano-5-methylthio-1*H*-2-pyrrolecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (4.5 g, 45 mmol) in abs. EtOH (60 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (300 mL), the precipitate is separated by filtration and washed with water. Yield: 2.7 g (55 %), mp 188-191 °C (EtOH) ; IR (KBr): 3296 br (NH), 2226 (CN), 1742 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 9.45 (1H, s, NH), 4.29 (4H, m, OCH_2, SCH_2), 2.61 (3H, s, SCH_3), 1.08 (3H, t, *J* =7.0 Hz, CH_3); *Anal.* Calcd for $C_{12}H_{12}N_4O_3S_2$: C, 44.43; H, 3.73; N, 17.27; S, 19.77. Found: C, 44.80; H, 4.06; N, 16.93; S, 19.58.

(2-Methylthio-7-oxo-6,7-dihydrothiazolo[4,5-*d*]pyrimidin-5-ylsulfanyl)acetic acid ethyl ester (**14**)

A suspension of **13** (2.95 g, 10 mmol, prepared from 4-amino-2-methylthio-5-thiazolecarboxylic acid ethyl ester by chloroacetylation according to the general method)[15] and potassium thiocyanate (3.0 g, 30 mmol) in abs. EtOH (60 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (200 mL), the precipitate is separated by filtration and washed with water. Yield: 2.45 g (73 %), mp

140-143 °C ($MeNO_2$); IR (KBr): 3450, 3250 (NH), 1706 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 12.05 (1H, s, NH), 4.21 (2H, q, *J* =7.0 Hz, OCH_2), 3.99 (2H, s, SCH_2), 2.72 (3H, s, SCH_3), 1.24 (3H, t, *J* =7.0 Hz, CH_3); *Anal.* Calcd for $C_{10}H_{11}N_3O_3S_3 \cdot H_2O$: C, 35.81; H, 3.91; N, 12.53; S, 28.67. Found: C, 36.10; H, 3.67; N, 12.80; S, 28.19.

***N*-(1-Piperidinylcarbonyl)-*S*-(ethoxycarbonylmethyl)isothiourea** (**15**)

A solution of **14** (3.17 g, 10 mmol) in piperidine (10 mL) is heated to reflux for 20 h. After cooling the reaction mixture is poured into water (200 mL), the precipitate is separated by filtration and washed with water. Yield: 1.5 g (55 %), mp 139-141 °C (EtOH); IR (KBr): 3426, 3307 (NH_2), 1645, 1614 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 6.75 (2H, s, NH_2), 4.10 (2H, q, *J* =6.9 Hz, OCH_2), 3.45 (2H, s, SCH_2), 1.55 (10H, m, piperidinyl-H), 1.20 (3H, t, *J* =6.9 Hz, CH_3); ^{13}C-NMR (DMSO-d_6) δ : 169.98 (s, C-1), 23.46 (2t, C-2 and C-7), 163.8 and 163.4 (2s, C-3 and C-4), 48.37 (t, C-5 and C-5´), 24.78 (t, C-6 and C-6´), 58.62 (t, C-8), 14.68 (q, C-9) ppm; *Anal.* Calcd for $C_{11}H_{19}N_3O_3S$: C, 48.33; H, 7.00; N, 15.37; S, 11.73. Found: C, 48.82; H, 6.99; N, 15.88; S, 12.02.

2-(2-Imino-4-oxothiazol-3-yl)acetophenone (**17a**)

A suspension of **16a** (4.22 g, 20 mmol, prepared from 2-aminoacetophenone by chloroacetylation according to the general method)[15] and potassium thiocyanate (6.0 g, 60 mmol) in abs. EtOH (60 mL) is heated to reflux for 8 h. After cooling the reaction mixture is poured into water (200 mL), the precipitate is separated by filtration and washed with water. Yield: 2.0 g (43 %), mp 230-235 °C ($MeNO_2$/MeOH); IR (KBr): 3400 (NH), 1727, 1656 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 7.52-8.05 (4H, m, benzo-H), 4.12 (2H, s, SCH_2), 2.68 (3H, s, CH_3), NH signal not detected (br, > 12 ppm); *Anal.* Calcd for $C_{11}H_{10}N_2O_2S$: C, 56.40; H, 4.30; N, 11.96; S, 13.68. Found: 56.03; H, 4.31; N, 11.96; S, 13.50.

5-Chloro-2-(imino-4-oxothiazol-3-yl)benzophenone (**17b**)

A suspension of **16b** (3.08 g, 10 mmol, prepared from 2-amino-5-chlorobenzophenone by chloro-acetylation according to the general method)[15] and potassium thiocyanate (3.0 g, 30 mmol) in MeCN (60 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (300 mL), the precipitate is separated by filtration and washed with water. Yield: 1.1 g (33 %), mp 204-207 °C ($MeNO_2$); IR (KBr): 3454 (NH), 1731, 1650 (CO) cm^{-1}; *Anal.* Calcd for $C_{16}H_{11}N_2O_2ClS$: C, 58.10; H, 3.35; N, 8.47; Cl, 10.72; S, 9.69. Found: C, 58.39; H, 3.44; N, 8.41; Cl, 10.73; S, 9.62.

(4-Methylquinazolin-2-ylsulfanyl)-*N*-benzylacetamide (**18a**)

17a (2.34 g, 10 mmol) in a mixture of abs. EtOH (3 mL) and benzylamine (5 mL, 50 mmol) are heated to reflux for 8 h. After cooling the reaction mixture is diluted with water (70 mL) on which a yellow oil deposits. The solidified material is separated by filtration and washed with water. Yield: 0.8 g (25 %), mp 110-112 °C (EtOH); IR (KBr): 3288 (NH), 1651, 1547 (CO, secondary amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 8.68 (1H, t, *J* =5.7 Hz, NH), 7.53-8.15 (4H, m, benzo-H), 7.21 (5H, m, phenyl-H), 4.31 (2H, d, *J*

=5.7 Hz, CH_2), 4.01 (2H, s, SCH_2), 2.84 (3H, s, CH_3); *Anal*. Calcd for $C_{18}H_{17}N_3OS$: C, 66.85; H, 5.30; N, 12.99; S, 9.91. Found: C, 66.77; H, 5.38; N, 12.85; S, 9.68.

(6-Chloro-4-phenylquinazolin-2-ylsulfanyl)-*N*-benzylacetamide (**18b**)

17b (3.30 g, 10 mmol) in a mixture of abs. EtOH (10 mL) and benzylamine (5 mL, 50 mmol) is heated to reflux for 15 h. After cooling the reaction mixture is poured into water (100 mL), the precipitate is separated by filtration and washed with water. Yield: 1.7 g (40 %), mp 193-196 °C (n-BuOH); IR (KBr): 3306 (NH), 1638, 1557 (CO, secondary amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 8.71 (1H, t, *J* =5.8 Hz, NH), 7.72-8.06 (5H, m, phenyl-H), 7.60 (3H, m, benzo-H), 7.20 (5H, m, phenyl-H), 4.33 (2H, d, *J* =5.8 Hz, NCH_2), 4.08 (2H, s, SCH_2); *Anal.* Calcd for $C_{23}H_{18}N_3OClS$: C, 65.78; H, 4.32; N, 10.01; Cl, 8.44; S, 7.63. Found: C, 65.72; H, 4.37; N, 9.89; Cl, 8.72; S, 7.37.

6-Chloro-2-(morpholin-4-yl)-4-phenylquinazoline (**19**)

17b (3.3 g, 10 mmol) is heated to reflux in a mixture of absolute EtOH (5 mL) and morpholine (10 mL, 115 mmol) for 4 h. After cooling the reaction mixture is diluted with water (10 mL), the precipitate is separated by filtration and washed with *n*-propanol. Yield: 0.7 g (21 %), mp 163-165 °C(EtOH); ^{1}H - NMR (DMSO-d_6) δ : 7.71 (8H, m, benzo-H, phenyl-H), 3.72 (8H, m, $2NCH_2$, $2OCH_2$); *Anal.* Calcd for $C_{18}H_{16}N_3OCl$: C, 66.36; H, 4;94; N, 12.89; Cl, 10.88. Found: C, 66.12; H, 4.86; N, 12.66; Cl, 10.92.

(7-Methyl-2-methylthiothiazolo[4,5-*d*]pyrimidin-5-ylsulfanyl)acetic acid ethyl ester (**21**)

A suspension of **20** (12.5 g, 47 mmol, prepared from 4-amino-2-methylthio-5-thiazolyl methyl ketone by chloroacetylation according to the general method)[15] and potassium thiocyanate (14.0 g, 140 mmol) in abs. EtOH (200 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (500 mL), the precipitate is separated by filtration and washed with water. Yield: 8.4 g (61 %),mp 93-94 °C (EtOH); IR (KBr): 1744 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 4.14 (2H, q, *J* =7.0 Hz, OCH_2), 4.05 (2H, s, SCH_2), 2.84 (3H, s, CH_3), 2.61 (3H, s, SCH_3), 1.20 (3H, t, *J* =7.0 Hz, CH_3); *Anal.* Calcd for $C_{11}H_{13}N_3O_2S_3$: C, 41.89; H, 4.15; N, 13.32; S, 30.49. Found: C, 41.89; H, 4.19; N, 13.33; S, 30.47.

(2-Hydrazino-7-methylthiazolo[4,5-*d*]pyrimidin-5-ylsulfanyl)acetic acid hydrazide (**22a**)

21 (1.43 g, 4.5 mmol) is stirred in a mixture of EtOH (4 mL) and hydrazine hydrate (5 mL, 80 %, 80 mmol) for 7 h at rt. Subsequently, the reaction mixture is poured into water (100 mL), the precipitate is separated by filtration and washed with water. Yield: 0.8 g (62 %), mp 225-226 °C (DMF); IR (KBr): 3360-3120 (NH, NH_2), 1682, 1553 (CO, amide) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 10.22 (1H, s, NH), 9.20 (1H, s, NH), 5.38 (2H, s, NH_2), 4.33 (2H, s, NH_2), 3.84 (2H, s, SCH_2), 2.45 (3H, s, CH_3); *Anal.* Calcd for $C_8H_{11}N_7OS_2$: C, 33.67; H, 3.89; N, 34.36; S, 22.47. Found: C, 33.35; H, 4.16; N, 34.28; S, 22.37.

[7-Methyl-2-(morpholin-4-yl)thiazolo[4,5-*d*]pyrimidin-5- ylsulfanyl]acetic acid ethyl ester (**22b**)

21 (2.86 g, 9 mmol) dissolved in a mixture of EtOH (5 mL) and morpholine (10 mL, 115 mmol) was heated to reflux for 16 h. After cooling the reaction mixture is poured into ice water (100 mL), the

precipitate is separated by filtration and washed with water. Yield: 1.4 g (44 %), mp 163-165 °C (EtOH); IR (KBr): 1744 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 4.12 (2H, q, J =7.0 Hz, OCH_2), 3.97 (2H, s, SCH_2), 3.70 (8H, m, $2NCH_2$, $2OCH_2$), 2.45 (3H, s, CH_3), 1.19 (3H, t, J =7.0 Hz, CH_3); EI-MS *m/z* : 355 (M^+). *Anal.* Calcd for $C_{14}H_{18}N_4O_3S_2$: C, 47.44; H, 5.12; N, 15.81; S, 18.09. Found: C, 47.75; H, 5.25; N, 15.78; S, 17.90.

(7-Methyl-1-phenylimidazolo[4,5-*d*]pyrimidin-5-ylsulfanyl)acetic acid ethyl ester (**24**)

A suspension of **23** (2.78 g, 10 mmol, prepared from 4-amino-1-phenyl-*1H*-imidazolyl methyl ketone by chloroacetylation according to the general method)[15] and potassium thiocyanate (3.0 g, 30 mmol) in abs. EtOH (50 mL) is heated to reflux for 3 h. After cooling the reaction mixture is poured into water (150 mL), the precipitate is separated by filtration and washed with water. Yield: 1.5 g (46 %), mp 113-116 °C (EtOH); IR (KBr): 1727 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ : 8.71 (1H, s, CH), 7.60 (5H, m, phenyl-H), 4.12 (2H, q, J =7.0 Hz, OCH_2), 4.02 (2H, s, SCH_2), 2.24 (3H, s, CH_3), 1.20 (3H, t, J =7.0 Hz, CH_3); El-MS *m/z* : 329 (M^+). *Anal.* Calcd for $C_{16}H_{16}N_4O_2S$: C, 58.52; H, 4.91; N, 17.06, S, 9.76. Found: C, 58.46; H, 4.94; N, 16.72; S, 9.84.

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