Selective Nucleophilic Replacement of the Benzylsulfanyl Group in 2,4-Disulfanyl-substituted Thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Derivatives by Secondary Amines

Detlef Briel

Fakultät für Biowissenschaften, Pharmazie und Psychologie der Universität Leipzig, Institut für Pharmazie, Pharmazeutische Chemie, Brüderstraße 34, 04103 Leipzig

Simon Drescher and Bodo Dobner*

Fachbereich Pharmazie der Martin-Luther-Universität Halle/Wittenberg, Institut für Pharmazeutische Chemie, Wolfgang-Langenbeck-Straße 4, 06120 Halle/Saale

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Thieno[2,3-*d*]pyrimidines with benzylsulfanyl and allylsulfanyl group in the presence of other alkylsulfanyl substituents react selectively under mild conditions with secondary amines under replacement of the benzyl or allyl residue whereas the other substituents remain intact. This enables the synthesis of different basic substituted derivatives with potentially biologically activity.

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In a former publication [1] we have reported an effective and short synthesis of 6-methylsulfanyl-2,4-dithioxo-1,2,3,4-tetrahydropyrimidin-5-carbonitrile **1** and some reactions of this compound.

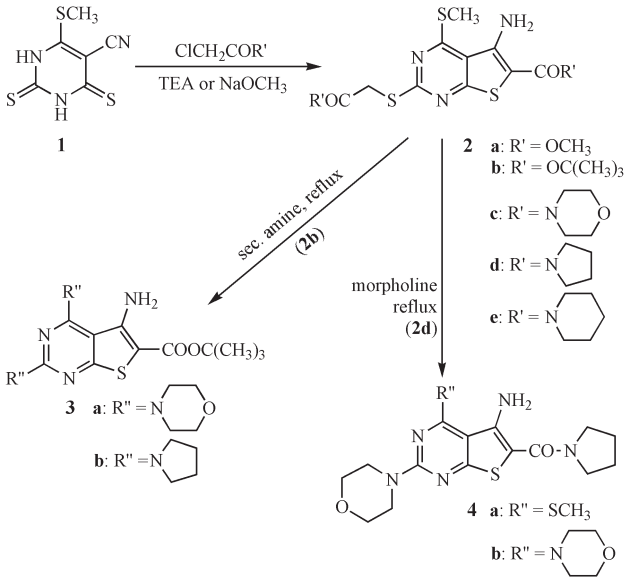
Whereas the reaction of the 2,4,6-trimethylsulfanylpyrimidin-5-carbonitrile resulting from the reaction of **1** and methyl iodide with secondary amines gives amino substituted pyrimidines, the alkylation reaction of **1** with chloroacetic acid derivatives using sodium methoxide and/or triethyl amine as base yield 2,4-disulfanyl substituted 5-aminothieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives **2** [1].

Now we present our results regarding the selective nucleophilic substitution of the benzylsulfanyl group in the 2,4-disulfanyl substituted thieno[2,3-*d*]pyrimidine system. Since the thiophene ring is a bioisoster to benzene the thieno[2,3-*d*]pyrimidines should have similar properties as quinazolines which are interesting because of their known biological activity. Basic substituted quinazolines were found to be targets for tyrosin kinases [2]. The inhibition of these kinases is of outstanding interest with regard to cancer treatment. However there is a strong relationship between structural variations and the selectivity on certain tyrosinkinases of substances active in this regard. Therefore the search for new compounds with potential effect on tyrosinkinases is of great interest in this important field of medical chemistry.

Starting from compound **1** we have synthesized two new thieno[2,3-*d*]pyrimidin-6-carboxylic acid amides **2d** and **2e**. In a model reaction we have first investigated the nucleophilic substitution by heating of **2b** with the secondary amines morpholine and pyrrolidine without solvent. In this reaction compound **3a** and **3b** were isolated in 77% and 85% yield, respectively. However the reaction of **2d** with morpholine under the same conditions gives a mixture of the mono- and disubstituted compounds **4a** and **4b** (Scheme 1). This is due to the stronger electron withdrawing influence of the ester group compared to the amide residue in the 6-position of the thieno[2,3-*d*]pyrimidine. This was also found for compound **2a** [1].

But our aim was the selective replacement of only one thiofunction by an amino substituent. A mono substitution in the 4-position of the thieno[2,3-*d*]pyrimidine system enables the selective variation of all three substituents to deliver a broad substance pool for further biological tests. The application of milder conditions led to mixtures in all cases which could sometimes be separated with heavy losses. So the methylsulfanyl function in position four was not suitable. Several attempts to enhance the reactivity by transforming the methylsulfanyl group into the corre-

Scheme 1



sponding sulfoxide or sulfone which is a better leaving group shown by some authors [3] failed. The reason for that was that a selective oxidation was missing.

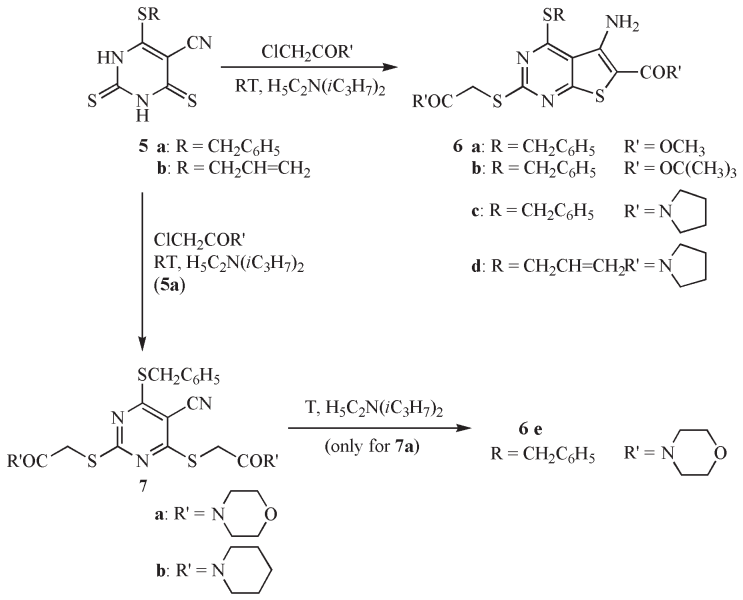
In some earlier attempts to synthesise thieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives from 4-benzylsulfanyl or 4-allylsulfanyl groups (**5a**, **b**) we found that with strong alkoxide bases beside the cyclisation to compounds **6a** substitution by the alkoxide molecule has taken place. This was not observed starting from compound **1**. Therefore we could assume the higher reactivity of benzylsulfanyl or allylsulfanyl group. For studying these nucleophilic replacements the synthesis of appropriate thieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives was necessary. Alkylation reaction proceeds smoothly at room temperature using Hünig's base starting from **5a** or **b** to get thieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives **6a-d** in respectable yields between 56% and 87%. However no cyclisation to this heterobicyclic system was observed in the case when **5a** was alkylated with chloroacetic acid morpholide and chloroacetic acid piperidide using the above discussed conditions. After heating the monocyclic compounds **7** only **7a** gives the bicyclic substance **6e** (Scheme 2).

tives (**8**). The difference with respect to the products which were isolated from **2a** was that the side chain was not separated during the reaction. Only the methoxy group in the ester function in the 2-position of the bicyclic system was transformed in the corresponding amide structure. This was concluded from the analysis of the mass spectra. So there was found a fragment peak assigned to the fragmentation of the side chain in the 2-position (m/z 277) including the sulfur atom of the heterobicyclic system. The corresponding fragment with a methoxycarbonylmethylsulfanyl residue could not be detected. The same situation was found in the reaction of **2a** with piperidine indicating the higher stability of the ester function bound directly to the thiophene ring system. The separation of the mixtures is possible by recrystallisation or chromatography.

In the case of compounds **6b**, **c** and **e** selective replacement of the benzylsulfanyl group in the 4-position takes place and the corresponding amino substituted derivatives were isolated in good yields. The substances prepared after that procedure are shown in Scheme 3. However our investigations failed in the case of primary amines like aniline.

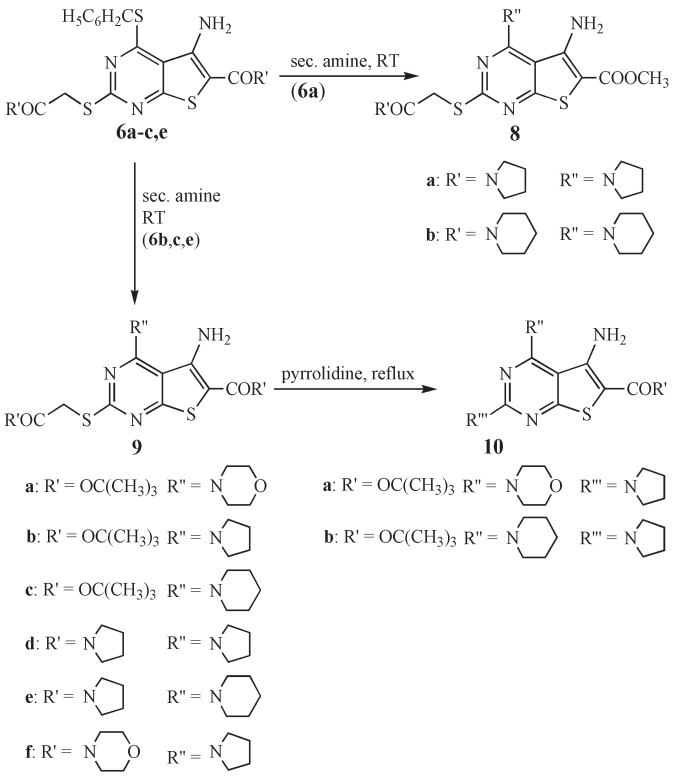
On the other hand compounds **9** were transformed selec-

Scheme 2



For the investigation of the nucleophilic substitution reaction we have used only 4-benzylsulfanyl substituted thieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives. This is due to the low to moderate yield obtained for the synthesis of **5b** [4]. Starting from compound **6a** the reaction with cyclic secondary amines gave a mixture of monosubstituted (in position 4) and disubstituted derivatively into substituted thieno[2,3-*d*]pyrimidin-6-carboxylic acid derivatives (**10**) in high yields (about 90%) with three different functions by heating with secondary amines. Since the yields for these transformations are good the method enables us to synthesize a broad spectrum of different functionalised thieno[2,3-*d*]pyrimidin-6-yl carboxylic acid derivatives.

Scheme 3



EXPERIMENTAL

Melting points were acquired with a Boetius apparatus and are uncorrected. The ^{1}H and ^{13}C nmr spectra have been recorded on a Varian Gemini 2000 or Varian Inova 500 using tetramethylsilane as internal reference. Chemical shifts are given in ppm. Mass spectrometric data were obtained on an AMD 402 (70eV) spectrometer (Intecta GmbH, Harpstedt). Elemental analyses were performed with a CHNS-932 apparatus (LECO-Corporation, St. Joseph, Michigan USA). Infrared spectra were obtained on a FT-IR spectrometer IFS 28 (Bruker Optik, Ettlingen).

The chloroacetic acid amides were prepared according to literature [5]. Chloroacetic acid methylester and chloroacetic acid *tert*-butylester were purchased from Aldrich.

New Thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Amides (**2d** and **e**).

To 5 mmol of the pyrimidine **1** (1.08 g) in 20 ml dry methanol were added 8 mmol (1.6 ml) sodium methoxide (5 *M*) and 8 mmol of the chloroacetic acid amides at room temperature. After 2 days the yellow precipitate was collected by suction filtration, recrystallised from 2-methoxyethanol and dried *in vacuo*.

5-Amino-4-methylsulfanyl-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**2d**).

Compound **2d** was obtained from compound **1** in reaction with chloroacetic acid pyrrolidide in 65% yield (1.42 g); mp: 221-222 °C; ir: 3432, 3233, 2980, 2960, 2880, 1633, 1563, 1514, 1394 cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 1.8-2.0 (m, 8H, 2x –CH_2(C**H**$_2$)$_2$$CH_2$–), 2.68 (s, 3H, –SC$H_3$), 3.5-3.7 (m, 8H, 2x –C$H_2NCH_2$–), 4.03 (s, 2H, –COC$H_2$S–), 6.74 (s, 2H, –N$H_2$); ^{13}C nmr (100 MHz, deuteriochloroform): δ 12.75 (–S*C*H$_3$), 34.87 (–CO*C*H$_2$S–), 147.07 (–*C*NH$_2$); ms: m/z 437 (M$^+$, 100%), 367 (30%), 326 (52%).

Anal. Calcd. for $C_{18}H_{23}N_5O_2S_3$: C, 49.40; H, 5.30; N, 16.01; S, 21.98. Found: C, 49.53; H, 5.27; N, 15.64; S, 21.88.

5-Amino-4-methylsulfanyl-2-(piperidinocarbonylmethylsulfanyl)thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Piperidide (**2e**).

Compound **2e** was obtained from compound **1** in reaction with chloroacetic acid piperidide in 62% yield (1.44 g); mp: 161-162 °C; ir: 3447, 3424, 3242, 2938, 2925, 2856, 1639, 1557, 1511, 1405, 1258 cm^{-1}; ^{1}H nmr (500 MHz, deuteriochloroform): δ 1.6-1.7 (m, 12H, 2x –CH_2(CH_2)$_3$$CH_2$–), 2.69 (s, 3H, –SC$H_3$), 3.5-3.6 (m, 8H, 2x –C$H_2NCH_2$–), 4.14 (s, 2H, –COC$H_2$S–), 6.00 (s, 2H, –N$H_2$); ^{13}C nmr (125 MHz, deuteriochloroform): δ 12.67 (–S*C*H$_3$), 34.11 (–CO*C*H$_2$S–), 145.30 (–*C*NH$_2$); ms: m/z 465 (M$^+$, 73%), 381 (20%), 340 (24%), 84 (100%).

Anal. Calcd. for $C_{20}H_{27}N_5O_2S_3$: C, 51.59; H, 5.85; N, 15.04; S, 20.66. Found: C, 51.58; H, 5.82; N, 15.10; S, 20.91.

Reaction of Compound **2b** with Secondary Amines.

Compound **2b** (0.21 g, 0.5 mmol) and 5 ml secondary amine were heated 3 hours under reflux. After cooling to room temperature 10 ml methanol and 20 ml water were added. The precipitate was collected by suction filtration, recrystallised from 2-methoxyethanol and dried *in vacuo*.

5-Amino-2,4-dimorpholinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**3a**).

Compound **3a** was obtained from compound **2b** and morpholine in 77% yield (0.16 g); mp: 187-189 °C; ir: 3456, 3341, 2970, 2881, 2843, 1656, 1250, 1113 cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 1.54 (s, 9H, –C(CH_3)$_3$), 3.37, 3.74-3.75 and 3.84 (3m, 16H, 2x –N(C_2H_4)$_2$O), 6.09 (s, 2H, –NH_2); ^{13}C nmr (100 MHz, deuteriochloroform): δ 146.98 (–*C*NH$_2$); ms: m/z 421 (M$^+$, 30%), 365 (100%).

Anal. Calcd. for $C_{19}H_{27}N_5O_4S$: C, 54.14; H, 6.46; N, 16.62; S, 7.61. Found: C, 53.80; H, 6.29; N, 16.61; S, 7.80.

5-Amino-2,4-dipyrrolidinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**3b**).

Compound **3b** was obtained from compound **2b** and pyrrolidine in 85% yield (0.17g); mp: 173-174 °C; ir: 3417, 3314, 2970, 2862, 1656, 1520 cm^{-1}; ^{1}H nmr (200 MHz, deuteriochloroform): δ 1.53 (s, 9H, –C(CH_3)$_3$), 1.87-1.93 (m, 8H, 2x –CH_2(CH_2)$_2$$CH_2$–), 3.5-3.7 (m, 8H, 2x –CH_2NCH_2–), 5.96 (s, 2H, –NH_2); ms: m/z 389 (M$^+$, 35%), 333 (100%).

Anal. Calcd. for $C_{19}H_{27}N_5O_2S$: C, 58.59; H, 6.99; N, 17.98; S 8.23. Found: C, 58.69; H 6.81; N, 17.78; S, 8.07.

Synthesis of 5-Amino-4-methylsulfanyl-2-morpholinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**4a**) and 5-Amino-2,4-dimorpholinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**4b**).

Compound **2d** (0.22 g, 0.5 mmol) and 3 ml morpholine were heated for 2 hours under reflux. After cooling to room temperature 10 ml dry methanol were added. The precipitate was collected by suction filtration after one day. Compounds **4a** and **4b** were separated by column chromatography (silica gel 60 Merck, 0.063-0.2 mm) with chloroform and methanol using gradient

technique (starting with $CHCl_3$, final polarity $CHCl_3$/MeOH = 9:1).

5-Amino-4-methylsulfanyl-2-morpholinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**4a**).

Compound **4a** was obtained in 38% yield (0.07 g); mp: 232-233 °C; ir: 3454, 3274, 2972, 2870, 1570, 1543, 1398, 1271, 1116 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): δ 1.90-1.93 (m, 4H, $-CH_2(CH_2)_2CH_2-$), 2.63 (s, 3H, $-SCH_3$), 3.66-3.69 (m, 4H, $-CH_2NCH_2-$ from pyrrolidine), 3.74-3.76 and 3.85-3.87 (2t, 8H, $-N(C_2H_4)_2O$), 6.77 (s, 2H, $-NH_2$); ^{13}C nmr (125 MHz, deuteriochloroform): δ 12.51 ($-SCH_3$), 148.02 ($-CNH_2$); ms: m/z 379 (M^+, 100%), 309 (57%), 282 (44%).

Anal. Calcd. for $C_{16}H_{21}N_5O_2S_2$: C, 50.64; H, 5.58; N, 18.46; S, 16.90. Found: C, 50.53; H, 5.46; N, 18.42; S, 16.72.

5-Amino-2,4-dimorpholinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**4b**).

Compound **4b** was obtained in 24% yield (0.05 g); mp: 243-244 °C; ir: 3445, 3300, 2962, 2924, 2854, 1557, 1422, 1261, 1117 cm^{-1}; ^1H nmr (200 MHz, deuteriochloroform): δ 1.88-1.95 (m, 4H, $-CH_2(CH_2)_2CH_2-$), 3.34-3.38 and 3.64-3.85 (2m, 20H, $-CH_2NCH_2-$ and 2x $-N(C_2H_4)_2O$), 6.61 (s, 2H, $-NH_2$); ms: m/z 418 (M^+, 100%), 348 (27%), 321 (36%).

Anal. Calcd. for $C_{19}H_{26}N_6O_3S$: C, 54.53; H, 6.26; N, 20.08; S, 7.66. Found: C, 54.62; H, 6.12; N, 20.16; S, 7.52.

General Procedure for the Synthesis of 4-Allylsulfanyl or 4-Benzylsulfanyl Thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Derivatives (**6a-d**).

To 10 mmol of the pyrimidine (**5a** or **5b**) in 50 ml dry methanol were added 20 mmol Hünig's base (2.58 g) and 20 mmol of the chloroacetic acid derivatives. After standing 3 days at room temperature the precipitate was collected by suction filtration, recrystallised from 2-methoxyethanol and dried *in vacuo*.

5-Amino-4-benzylsulfanyl-2-(methoxycarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Methylester (**6a**).

Compound **6a** was obtained from compound **5a** in reaction with chloroacetic acid methylester in 71% yield (3.09 g); mp: 176-177 °C; ir: 3453, 3344, 2983, 2929, 2853, 1745, 1667, 1530, 1277 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 3.73 and 3.84 (2s, 6H, 2x $-OCH_3$), 3.98 (s, 2H, $-COCH_2S\_$), 4.62 (s, 2H, $-SCH_2C_6H_5$), 6.42 (s, 2H, $-NH_2$), 7.26-7.42 (m, 5H, $-C_6H_5$); ms: m/z 435 (M^+, 100%), 362 (38%).

Anal. Calcd. for $C_{18}H_{17}N_3O_4S_3$: C, 49.64; H, 3.94; N, 9.65; S, 22.08. Found: C, 49.80; H, 4.00; N, 9.67; S, 22.70.

5-Amino-4-benzylsulfanyl-2-(*tert*-butoxycarbonylmethylsulfanyl)thieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**6b**).

Compound **6b** was obtained from compound **5a** in reaction with chloroacetic acid *tert*-butylester in 87% yield (4.5 g); mp: 158-160 °C; ir: 3459, 3339, 2978, 2936, 1730, 1667, 1525 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): δ 1.45 and 1.54 (2s, 18H, 2x $-C(CH_3)_3$), 3.86 (s, 2H, $-COCH_2S-$), 4.62 (s, 2H, $-SCH_2C_6H_5$), 7.27-7.42 (m, 5H, $-C_6H_5$); ^{13}C nmr (125 MHz, deuteriochloroform): δ 34.13 and 34.76 (2x $-SCH_2-$), 81.73 and 82.11 (2x $-C(CH_3)_3$); ms: m/z 519 (M^+, 56%), 463 (62%), 407 (100%).

Anal. Calcd. for $C_{24}H_{29}N_3O_4S_3$: C, 55.47; H, 5.63; N, 8.09; S, 18.51. Found: C, 55.67; H, 5.48; N, 8.07; S, 18.91.

5-Amino-4-benzylsulfanyl-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**6c**).

Compound **6c** was obtained from compound **5a** in reaction with chloroacetic acid pyrrolidide in 75% yield (3.85 g); ir: 3439, 3242, 3059, 3035, 2969, 2952, 2873, 1637, 1550, 1512 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.84-1.95 (m, 8H, 2x $-CH_2(CH_2)_2CH_2-$), 3.5-3.7 (m, 8H 2x $-CH_2NCH_2-$), 4.04 (s, 2H, $-COCH_2S-$), 4.60 (s, 2H, $-SCH_2C_6H_5$), 7.23-7.42 (m, 5H, $-C_6H_5$); ms: m/z 513 (M^+, 77%), 401 (18%), 91 (100%).

Anal. Calcd. for $C_{24}H_{27}N_5O_2S_3$: C, 56.11; H, 5.30; N, 13.63; S, 18.72. Found: C, 56.20; H, 5.28; N, 13.65; S, 18.93.

4-Allylsulfanyl-5-amino-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**6d**).

Compound **6d** was obtained from compound **5b** in reaction with chloroacetic acid pyrrolidide in 56% yield (2.6 g); mp: 188 °C, dec.; ir: 3439, 3243, 3086, 2966, 2910, 2875, 1639, 1555, 1513 cm^{-1}; ^1H nmr (200 MHz, deuteriochloroform): δ 1.91-1.97 (m, 8H, 2x $-CH_2(CH_2)_2CH_2-$), 3.47-3,73 (m, 8H 2x $-CH_2NCH_2-$), 4.01-4.04 (d, 2H, $-SCH_2CH=$), 4.04 (s, 2H, $-COCH_2S-$), 5.16-5.40 (dd, 2H, $=CH_2$), 5.88-6.02 (m, 1H, $-CH=$); ms: m/z 463 (M^+, 95%), 351 (100%).

Anal. Calcd. for $C_{20}H_{25}N_5O_2S_3$: C, 51.81; H, 5.44; N, 15.11; S, 20.75. Found: C, 51.67; H, 5.35; N, 15.11; S, 20.72.

Synthesis of 2,4-disubstituted 6-Benzylsulfanylpyrimidin-5-carbonitrile (**7a** and **7b**).

Compound **5a** (10 mmol) was suspended in 50 ml dry methanol. After addition of 20 mmol of Hünig's base and 20 mmol of the chloroacetic acid derivatives the mixture was allowed to stand for 3 days at room temperature. The product was collected by suction filtration and recrystallised from 2-methoxyethanol.

6-Benzylsulfanyl-2,4-bis(morpholinocarbonylmethylsulfanyl)-pyrimidin-5-carbonitrile (**7a**)

Compound **7a** was obtained from compound **5a** in reaction with chloroacetic acid morpholide in 62% yield (3.4 g); mp: 194-195 °C; ir: 3017, 2935, 2862, 2215, 1662, 1587, 1503 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 3.40-3.72 (m, 16H, 2x $-N(C_2H_4)_2O$), 4.06 and 4.15 (2s, 4H, 2x $-COCH_2S-$), 4.44 (s, 2H, $-SCH_2C_6H_5$), 7.25-7.34 (m, 5H, $-C_6H_5$); ms: m/z 545 (M^+, 21%), 417 (38%), 91 (100%).

Anal. Calcd. for $C_{24}H_{27}N_5O_4S_3$: C, 52.82; H, 4.99; N, 12.83; S, 17.63. Found: C, 52.89; H, 5.07; N, 12.86; S, 18.18.

6-Benzylsulfanyl-2,4-bis(piperidinocarbonylmethylsulfanyl)-pyrimidin-5-carbonitrile (**7b**)

Compound **7b** was obtained from compound **5a** in reaction with chloroacetic acid piperidide in 58% yield (3.1 g); mp: 147-148 °C; ir: 3017, 2937, 2857, 2214, 1663, 1580, 1502 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): δ 1.53-1.64 (m, 12H, 2x $-CH_2(CH_2)_3CH_2-$), 3.35-3.54 (m, 8H, 2x $-CH_2NCH_2-$), 4.07 and 4.15 (2s, 4H, 2x $-COCH_2S-$), 4.44 (s, 2H, $-SCH_2C_6H_5$), 7.25-7.34 (m, 5H, $-C_6H_5$); ms: m/z 541 (M^+, 35%), 415 (26%), 91 (100%).

Anal. Calcd. for $C_{26}H_{31}N_5O_2S_3$: C, 57.64; H, 5.77; N, 12.93; S, 17.75. Found: C, 57.60; H, 5.85; N, 13.01; S, 17.48.

Procedure for the Conversion of Compound **7a** into **6e**.

Compound **7a** (3.0 g, 5.5 mmol) was suspended in 40 ml 2-methoxyethanol. After addition of 10 drops of Hünig's base the mixture was heated for 10 hours under reflux. After cooling to room temperature the precipitate was collected by suction filtration and recrystallised two times from methanol.

5-Amino-4-benzylsulfanyl-2-(morpholinocarbonylmethylsulfanyl)thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Morpholide (**6e**).

Compound **6e** was obtained in 40% yield (1.2 g); mp: 185 °C; ir: 3348, 3201, 3048, 3013, 2929, 2862, 1662, 1501, 1397, 1316, 1114 cm^{-1}; ^1H nmr (400MHz, deuteriochloroform): δ 3.58-3.71 (m, 16H, 2x $–N(C_2H_4)_2O$), 4.10 (s, 2H, $–COCH_2S–$), 4.61 (s, 2H, $–SCH_2C_6H_5$), 6.15 (s, 2H, $–NH_2$), 7.26-7.50 (m, 5H, $–C_6H_5$); ms: m/z 545 (M^+, 100%), 458 (21%).

Anal. Calcd. for $C_{24}H_{27}N_5O_4S_3$: C, 52.82; H, 4.99; N, 12.83; S, 17.63. Found: C, 52.64; H, 4.83; N, 12.67; S, 17.91.

General Procedure for the Reaction of **6a** with Secondary Amines.

In a flask 1 mmol of compound **6a** (0.44 g) were suspended in 20 ml of the corresponding secondary amine with occasionally stirring at room temperature. After 1 h for the reaction with pyrrolidine 2 h for piperidine and 6 h for morpholine, respively the reaction mixture was cooled down to -20 °C. At this temperature 20 ml methanol were added and the temperature was than allowed to come to room temperature. After addition of 20 to 30 ml water the precipitate was collected by suction filtration, recrystallised two times from methanol and dried *in vacuo*.

5-Amino-4-pyrrolidino-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Methylester (**8a**).

Compound **8a** was obtained from **6a** and pyrrolidine in 63% yield (0.27 g); mp: 225-227 °C; ir: 3399, 3339, 3203, 2971, 2952, 2876, 1671, 1643, 1605, 1535, 1312 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): δ 1.82-1.88 and 1.98-2.01 (2m, 8H, 2x $–CH_2(CH_2)_2CH_2–$), 3.45-3.47 and 3.61-3.64 (2m, 8H, 2x $–CH_2NCH_2–$), 3.80 (s, 3H, $–OCH_3$), 3.94 (s, 2H, $–COCH_2S–$), 6.00 (s, 2H, $–NH_2$); ^{13}C nmr (125 MHz, deuteriochloroform): δ 34.51 ($–COCH_2S–$); ms: m/z 421 (M^+, 100%), 335 (60%).

Anal. Calcd. for $C_{18}H_{23}N_5O_3S_2$: C, 51.29; H, 5.50; N, 16.62; S, 15.21. Found: C, 51.06; H, 5.54; N, 16.59; S, 15.05.

5-Amino-4-piperidino-2-(piperidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Methylester (**8b**).

Compound **8b** was obtained from **6a** and piperidine in 24% yield (0.11 g); mp: 195-197°C; ir: 3461, 3344, 3195, 2938, 2856, 1672, 1646, 1593, 1540, 1280 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.55-1.72 (m, 12H, 2x $–CH_2(CH_2)_3CH_2–$), 3.36 and 3.54-3.58 (m, 8H, 2x $–CH_2NCH_2–$), 3.84 (s, 3H, $–OCH_3$), 4.11 (s, 2H, $–COCH_2S–$), 6.24 (s, 2H, $–NH_2$); ms: m/z 449 (M^+, 97%), 349 (100%).

Anal. Calcd. for $C_{20}H_{27}N_5O_3S_2$: C, 53.43; H, 6.05; N, 15.59; S, 14.26. Found: C, 53.43; H, 6.36; N, 15.56; S, 14.31.

Reaction of the 4-Benzylsulfanylthieno[2,3-*d*]pyrimidin-6-carboxylic Acid Derivatives **6b**,**c** and **e** with Secondary Amines.

In an Erlenmeyer flask 150 mg of the compounds **6b**,**c** or **e** were suspended in 6 ml of the respective secondary amine with occasionally stirring of the slurry at room temperature leading to a clear solution in most cases. After 2 h for the reaction with pyrrolidine and 20 h for piperidine and morpholine the mixture was cooled down to -20 °C. Than 10 ml methanol were added and the mixture was brought to room temperature. Subsequent adding of 20 ml water yields a precipitate which was collected by suction filtration, recrystallised from methanol/glycol mono methylether and dried *in vacou*.

5-Amino-2-(*tert*-butoxycarbonylmethylsulfanyl)-4-morpholino-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**9a**).

Compound **9a** was obtained from compound **6b** and morpholine in 73% yield (0.10 g); mp: 175-176 °C; ir: 3458, 3347, 3204, 2977, 2932, 2859, 1734, 1668, 1590, 1540, 1324, 1114 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.45 and 1.56 (2s, 18H, 2x $–C(CH_3)_3$), 3.44 (m, 4H, $–CH_2NCH_2–$), 3.82 (m, 4H, $–CH_2OCH_2–$), 3.84 (s, 2H,$–COCH_2S–$), 6.09 (s, 2H, $–NH_2$); ^{13}C nmr (100 MHz, deuteriochloroform): δ 34.81 ($–COCH_2S–$), 81.59 and 81.93 (2x $–C(CH_3)_3$); ms: m/z 482 (M^+, 53%), 426 (100%), 370 (39%).

Anal. Calcd. for $C_{21}H_{30}N_4O_5S_2$: C, 52.26; H, 6.27; N, 11.61; S, 13.29. Found: C, 52.32; H, 6.43; N, 11.61; S, 13.24.

5-Amino-2-(*tert*-butoxycarbonylmethylsulfanyl)-4-pyrrolidino-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**9b**).

Compound **9b** was obtained from compound **6b** and pyrrolidine in 84% yield (0.11 g); mp: 149-150 °C; ir: 3335, 3200, 2977, 2935, 1731, 1666, 1599, 1535, 1320, 1139 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.45 and 1.55 (2s, 18H, 2x $–C(CH_3)_3$), 1.90 (m, 4H, $–CH_2(CH_2)_2CH_2–$), 3.66 (m, 4H, $–CH_2NCH_2–$), 3.82 (s, 2H, $–COCH_2S–$), 5.90 (s, 2H, $–NH_2$); ms: m/z 466 (M^+, 58%). 410 (100%), 354 (50%).

Anal. Calcd. for $C_{21}H_{30}N_4O_4S_2$: C, 54.05; H, 6.48; N, 12.01; S, 13.74. Found: C, 54.08; H, 6.76; N, 12.07; S, 13.71.

5-Amino-2-(*tert*-butoxycarbonylmethylsulfanyl)-4-piperidino-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester (**9c**).

Compound **9c** was obtained from compound **6b** and piperidine in 71% yield (0.10 g); mp: 162-163°C; ir: 3463, 3348, 3209, 2978, 2936, 2856, 1736, 1667, 1590, 1539, 1324, 1285, 1141 cm^{-1}; ^1H nmr (400 MHz, deuteriochloroform): δ 1.45 and 1.55 (2s, 18H, 2x $–C(CH_3)_3$), 1.71 (m, 6H, $–CH_2(CH_2)_3CH_2–$), 3.34 (m, 4H, $–CH_2NCH_2–$), 3.84 (s, 2H, $–COCH_2S–$), 6.15 (s, 2H, $–NH_2$); ms: m/z 480 (M^+, 79%), 424 (100%), 368 (40%).

Anal. Calcd. for $C_{22}H_{32}N_4O_4S_2$: C, 54.97; H, 6.71; N, 11.66; S, 13.34. Found: C, 54.98; H, 6.84; N, 11.63; S, 13.28.

5-Amino-4-pyrrolidino-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**9d**)

Compound **9d** was obtained from compound **6c** and pyrrolidine in 68% yield (0.09 g); mp: 213-215 °C; ir: 3334, 3205, 2971, 2875, 1671, 1642, 1567, 1387 cm^{-1}; ^1H nmr (500 MHz, deuteriochloroform): δ 1.84-2.01 (m, 12H, 3x $–CH_2(CH_2)_2CH_2–$), 3.48-3.69 (m, 12H, 3x $–CH_2NCH_2–$), 4.01 (s, 2H, $–COCH_2S–$), 6.35 (s, 2H, $–NH_2$); ms: m/z 460 (M^+, 66%), 348 (100%), 277 (59%).

Anal. Calcd. for $C_{21}H_{28}N_6O_2S_2$: C, 54.76; H, 6.13; N, 18.25; S, 13.92. Found: C, 54.57; H, 6.27; N, 17.77; S, 13.62.

5-Amino-4-piperidino-2-(pyrrolidinocarbonylmethylsulfanyl)-thieno[2,3-*d*]pyrimidin-6-carboxylic Acid Pyrrolidide (**9e**)

Compound **9e** was obtained from compound **6c** and piperidine in 56% yield (0.08 g); mp: 165 °C dec.; ir: 3346, 3195, 2985,

2956, 2880, 1662, 1572, 1391 cm^{-1}; ^{1}H nmr (500MHz, deuteriochloroform): δ 1.65-1.99 (m, 14H, 2x –$CH_2(CH_2)_2CH_2$– and –$CH_2(CH_2)_3CH_2$–), 3.40-3.69 (m, 12H, 3x –CH_2NCH_2–), 4.05 (s, 2H, –$COCH_2S$–); ms: m/z 474 (M^+, 53%), 362 (100%), 291 (71%).

Anal. Calcd. for $C_{22}H_{30}N_6O_2S_2$: C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.23; H, 6.18; N, 17.62; S, 13.60.

5-Amino-2-(morpholinocarbonylmethylsulfanyl)-4-pyrrolidinothieno[2,3-*d*]pyrimidin-6-carboxylic Acid Morpholide (**9f**)

Compound **9f** was obtained from compound **6e** and pyrrolidine in 85% yield (0.11 g); mp: 124-126 °C; ir: 3349, 3197, 2942, 2866, 1653, 1617, 1559, 1397 cm^{-1}; ^{1}H nmr (500 MHz, deuteriochloroform): δ 1.91-1.93 (m, 4H, –$CH_2(CH_2)_2CH_2$–), 3.63-3.72 (m, 20H, –CH_2NCH_2– and 2x –$N(C_2H_4)_2O$), 4.08 (s, 2H, –$COCH_2S$–), 5.96 (s, 2H, –NH_2); ms: m/z 492 (M^+, 100%), 364 (62%).

Anal. Calcd. for $C_{21}H_{28}N_6O_4S_2$: C, 51.20; H, 5.73; N, 17.06; S, 13.02. Found: C, 51.14; H, 5.82; N, 16.91; S, 12.77.

Reaction of the 2,4-Disubstituted 5-Aminothieno[2,3-*d*]pyrimidin-6-carboxylic Acid *tert*-Butylester Derivatives **9a** and **c** with Pyrrolidine.

In a flask 100 mg of the compounds **9a** or **9c** were suspended in 5 ml pyrrolidine and were heated for 2 hours under reflux. After cooling to room temperature 5 ml methanol and 20 ml water were added, the precipitates were collected by suction filtration, recrystallised from methanol and dried *in vacou*.

5-Amino-4-morpholino-2-pyrrolidinolthieno[2,3-*d*]pyrimidine-6-carboxylic Acid *tert*-Butylester (**10a**)

Compound **10a** was obtained from compound **9a** and pyrrolidine in 90% yield (0.07 g); mp: 205.5-206.5 °C; ir: 3460, 3343, 3205, 2973, 2870, 1659, 1587, 1557, 1532, 1302, 1118 cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 1.54 (s, 9H, –$C(CH_3)_3$), 1.94-1.97 (m, 4H, –$CH_2(CH_2)_2CH_2$–), 3.35 (m, 4H, –CH_2NCH_2– from morpholine), 3.58-3.61 (m, 4H, –CH_2NCH_2– from pyrrolidine), 3.82-3,84 (m, 4H, –CH_2OCH_2–), 6.13 (s, 2H, –NH_2); ms: m/z 405 (M^+, 27%), 349 (100%).

Anal. Calcd. for $C_{19}H_{27}N_5O_3S$: C, 56.27; H, 6.71; N, 17.27; S, 7.91. Found: C, 56.03; H, 6.72; N, 17.57; S, 8.02.

5-Amino-4-piperidino-2-pyrrolidinothieno[2.3-*d*]pyrimidine-6-carboxylic Acid *tert*-Butylester (**10b**)

Compound **10b** was obtained from compound **9c** and pyrrolidine in 92% yield (0.07 g); mp: 187-188 °C; ir: 3459, 3341, 3193, 2975, 2936, 2870, 1660, 1586, 1553, 1320 cm^{-1}; ^{1}H nmr (400 MHz, deuteriochloroform): δ 1.54 (s, 9H, –$C(CH_3)_3$), 1.61 and 1.69-1.71 (m, 6H, –$CH_2(CH_2)_3CH_2$–), 1.93-1.96 (m, 4H, –$CH_2(CH_2)_2CH_2$–), 3.25 (m, 4H, –CH_2NCH_2– from piperidine), 3.58-3.61 (m, 4H, –CH_2NCH_2– from pyrrolidine), 6.20 (s, 2H, –NH_2); ms: m/z 403 (M^+, 46%), 347 (100%).

Anal. Calcd. for $C_{19}H_{27}N_5O_3S$: C, 59.53; H, 7.24; N, 17.36; S, 7.94. Found: C, 59.04; H, 7.24; N, 17.62; S, 7.87.

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