Selective Nucleophilic Substitution Reactions in 2,4,6-Trisulfanyl-substituted Pyrimidine-5-carbonitriles by Secondary Amines

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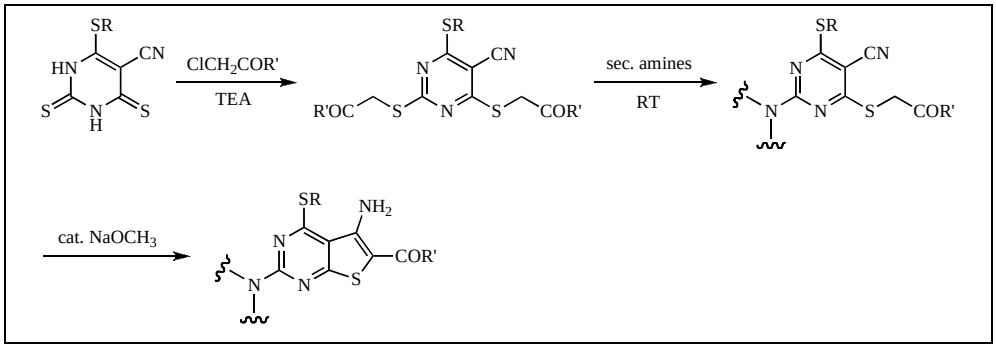

The highly functionalized heterocycles 6-alkyl- respectively 6-aralkylsulfanyl-2,4-bis-(amidomethyl-sulfanyl)pyrimidine-5-carbonitriles react selective in the 2-position with various secondary cyclic amines under mild conditions. The resulting pyrimidines were finally transformed into the corresponding thieno[2,3-*d*]pyrimidine-6-carboxylic acid amides which afford the synthesis of selective substituted thienopyrimidines.

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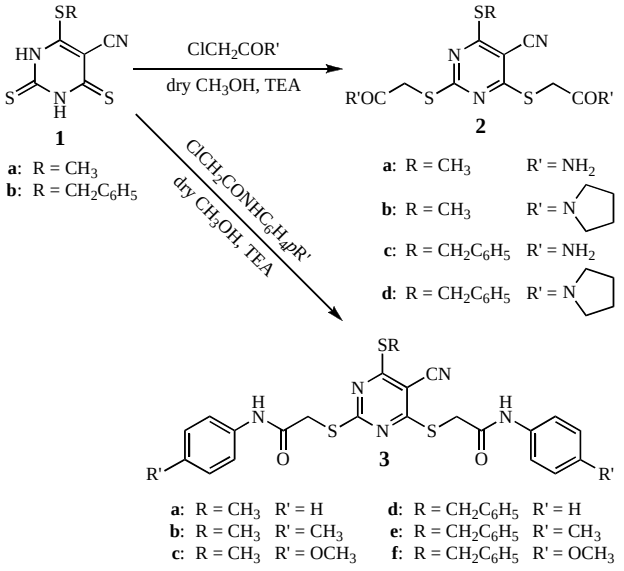
INTRODUCTION

Pyrimidines are an interesting class of heterocycles which possess numerous biological and pharmacological effects. Therefore this ring system is found in many pharmaceuticals, herbicides and fungicides [1]. Beside these applications conveniently functionalised pyrimidines are interesting initial compounds in heterocyclic synthesis.

Some time ago we published the synthesis of 6-methyl-sulfanyl-2,4-dithioxo-1,2,3,4-tetrahydropyrimidine-5-carbo-nitrile from simple starting compounds [2]. In that work we have also reported some results of alkylation reaction with electrophiles like alkyl halides, phenacyl bromides and halogeno acetic acid derivatives. In the case of the 2,4,6-trimethylsulfanylpyrimidine-5-carbonitrile some nucleophilic substitution reactions were studied under drastic conditions with low selectivity leading mainly to mixtures of products.

Now we report new results regarding to a selective nucleophilic substitution reaction at 2,4,6-trisulfanyl-substituted pyrimidine-5-carbonitriles under very mild conditions. For that purpose more new alkylation products of the 6-methylsulfanyl- and 6-benzylsulfanyl substituted 2,4-dithioxo-1,2,3,4-tetrahydropyrimidine-5-carbonitriles by reaction with aliphatic and aromatic 2-halogeno acetic acid amides were prepared. Thus the reaction of compound **1a** and **1b** with chloroacetic acid amides under mild conditions (room temperature) and with triethyl amine as base yielded the pyrimidine-5-carbonitriles **2** and **3** as shown in Scheme I. In contrast to triethyl amine the reaction with Hünig's base in the case of chloroacetic acid pyrrolidide results in alkylation and cyclisation to the corresponding thieno[2,3-*d*]pyrimidine [3].

Scheme I



We also found that the reaction of aromatic chloroacetic acid amides (to products **3**) was finished in shorter time

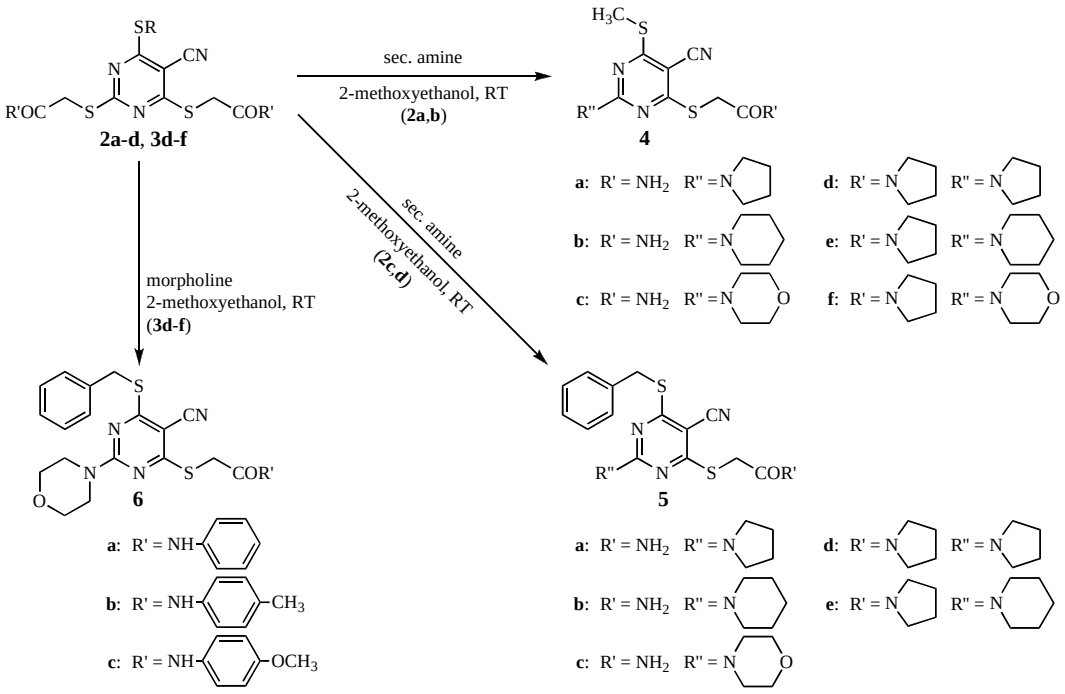
and in higher yields (53% to 80%) compared to the reaction of non-aromatic chloroacetic acid amides. This is due to the stronger electron withdrawing effect of the aromatic amides compared to the aliphatic amides. An influence of the 6-methylsulfanyl moiety compared to the 6-benzylsulfanyl moiety concerning alkylation reaction behaviour could not be found.

Scheme II shows the results of the reaction of compounds **2a**-**d** and **3d**-**f** with the secondary cyclic amines pyrrolidine, piperidine and morpholine in a suspension of 2-methoxyethanol under mild conditions at room temperature. In the case of the aliphatic amine residues in the amide structure of the substituents (**2a**-**d**) we isolated only one main product. The mass spectra indicate that one amidomethylsulfanyl residue was substituted by the secondary amine. The position of the substitution at the pyrimidine ring was determined by cyclisation reaction. The formation of the thieno[2,3-*d*]-pyrimidines **7** (see scheme III) is only possible if **2a**-**d** and **3d**-**f** react with the secondary cyclic amine in 2-position

Whereas the mono substitution reaction of compound **2** with secondary cyclic amines lead to pyrimidines **4** and **5** in a straightforward manner the pyrimidines with the aromatic amide residues (compounds **3d**-**f**) show a different reaction pattern. Only in the case of morpholine the mono substitution products **6a**-**c** could be isolated. The reaction of **3d**-**f** with pyrrolidine and piperidine results in a product mixture. Beside the expected pyrimidine the corresponding thieno-[2,3-*d*]pyrimidine and substitution products of the recent compound were detected by mass spectrometry. This is due to the higher basic strength of pyrrolidine and piperidine compared to morpholine which trigger the cyclisation and substitution reaction.

Furthermore we found that the thioether moiety in position 4 of the pyrimidine ring has no influence on the selectivity of the nucleophilic substitution. This is contrary to the substitution reaction at the 2,4-disulfanyl substituted thieno[2,3-*d*]-pyrimidine-6-carboxylic acid derivatives published previously [3]. In this case only the 4-benzylsulfanyl moiety was selective substituted by secondary cyclic amines at these

Scheme II



of the pyrimidine ring. Also a comparison of the ^{1}H nmr signals of the methylene groups in 2- and 4-position in the pyrimidine system and the corresponding thieno[2,3-*d*]-pyrimidine support this result to some extent.

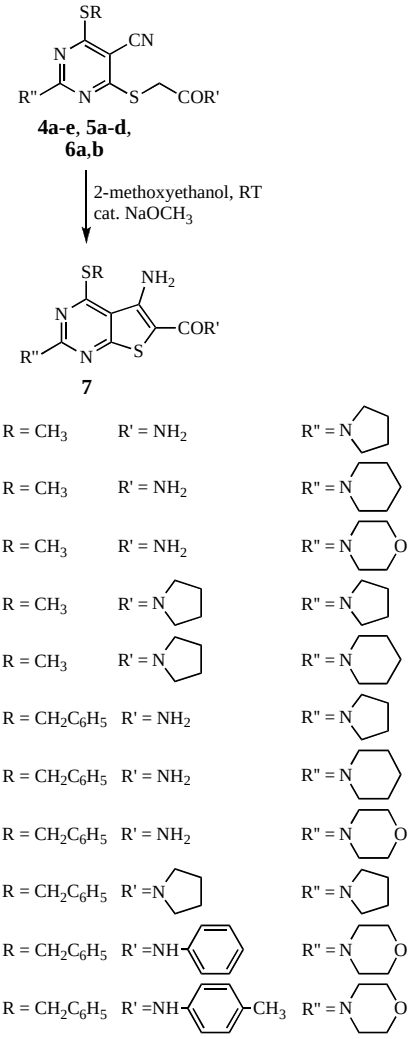
Furthermore the pyrimidines and thieno[2,3-*d*]-pyrimidines differ in their photoelectronic properties. Already during reaction monitoring of cyclisation using thin layer chromatography the appearance of strong fluorescence spots indicate the formation of the bicyclic heterocyclic system.

compounds. The presence of a methylsulfanyl group instead of the benzylsulfanyl residue leads to product mixtures. We found a substitution of the methylsulfanyl moiety beside the expected substitution of the substituent in 2-position [3].

The new pyrimidine-5-carbonitriles **4**, **5** and **6** with different functions were then suspended in 2-methoxyethanol with catalytic amounts of sodium methoxide yielding 5-amino-2-*sec*-amino-4-alkyl(aralkyl)sulfanyl-thieno[2,3-*d*]pyrimidine-6-carboxylic acid amides [**7a**-**k**] as shown in scheme III.

Due to the fact, that thieno[2,3-*d*]pyrimidines are bio-isoster to quinazolines these compounds become more important. It is known from this class of heterocycles that they have become interesting with regard to tyrosin kinase inhibitors [4]. The inhibition of these enzymes is now an accepted strategy in cancer therapy.

Scheme III



The results presented here enable not only the synthesis of highly functionalised pyrimidines with different substituents but also the synthesis of the corresponding thieno[2,3-*d*]pyrimidines. Moreover in connection with the selective substitution of the benzylsulfanyl group at the bicyclic system published previously [3] broad synthesis of new heterocyclic compounds with basic substituents are possible.

EXPERIMENTAL

Melting points were taken with a Boetius apparatus and are uncorrected. The ^{1}H nmr spectra have been recorded on a Varian Gemini 2000 (400 MHz) using deuteriochloroform as internal reference. Chemical shifts are given in ppm. Mass spectrometric data were obtained on an AMD 402 (70 eV) spectrometer (Intecta GmbH, Harpstedt). Static nanoES experiments were conducted on a qTOF mass spectrometer Q-TOF-2 (Waters/ Micromass, Manchester, UK) equipped with a nanoES Z-Spray source. The nanoES glass capillaries were obtained precoated from DNU-MS (Berlin, Germany). The TOF analyzer was calibrated externally using a mixture of sodium iodide and caesium iodide and internally using metasulam (analytical standard) as lock mass. The typical operating conditions for the qTOF mass spectrometer were as follows: capillary voltage, 900 V; sample cone voltage, 35 V; source temperature, 80°C. The instrument was operated in the positive ion mode. Full scans were performed over the *m/z* range of 50 to 1000. Elemental analyses were performed with a CHNS-932 apparatus (LECO-Corporation, St. Joseph, Michigan USA). Infrared spectra were obtained on a Spektrum BX FT-IR-system (Perkin Elmer).

The chloroacetic acid amides were prepared according to literature [5].

Reaction of Compound 1 with Various Chloroacetic Acid Amides.

General Procedure for the Preparation of Aliphatic Substituted 2,4-Bis-(aminocarbonylmethylsulfanyl)pyrimidine-5-carbonitriles (2a-d). To a suspension of 4.65 mmol of compound **1a** or **1b** in 30 ml dry methanol were added 9.30 mmol (0.94 g) TEA and 9.30 mmol of the respective chloroacetic acid amide. The reaction was allowed to stand over night at room temperature. After that time the precipitate was collected by suction filtration and recrystallized from 2-methoxyethanol.

2,4-Bis(aminocarbonylmethylsulfanyl)-6-methylsulfanyl-pyrimidine-5-carbonitrile (2a). Compound **2a** was obtained from compound **1a** in reaction with chloroacetic acid amide in 56% yield (0.86 g); mp: 252-255 °C; ir: 2972, 2923, 2212, 1665 cm^{-1}; ^{1}H nmr (DMSO-d6): δ 2.60 (s, 3H, -SC*H*$_3$), 3.90 (s, 2H, -SC*H*$_2$CO-), 3.99 (s, 2H, -COC*H*$_2$S-), 7.23-7.28 (d, 2H, *H*$_2$NCO-), 7.58-7.64 (d, 2H, -CON*H*$_2$); ms: m/z 329 (M$^+$, 100%), 312 (64%), 285 (65%). *Anal.* Calcd. for $C_{10}H_{11}N_5O_2S_3$: C, 36.46; H, 3.37; N, 21.26; S, 29.20. Found: C, 36.61; H, 3.50; N, 21.05; S, 29.58

6-Methylsulfanyl-2,4-bis(pyrrolidinocarbonylmethylsulfanyl)pyrimidine-5-carbonitrile (2b). Compound **2b** was obtained from compound **1a** in reaction with chloroacetic acid pyrrolidide in 68% yield (1.38 g); mp: 184-186 °C; ir: 2977, 2930, 2210, 1640 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.82-2.04 (m, 8H, 2x -CH$_2$(C*H*$_2$)CH$_2$-), 2.53 (s, 3H, -SC*H*$_3$), 3.44-3.62 (m, 8H, 2x -C*H*$_2$NC*H*$_2$-), 3.99 (s, 2H, -SC*H*$_2$CO-), 4.02 (s, 2H, -COC*H*$_2$S-); ms: m/z 437 (M$^+$, 50%) *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

2,4-Bis(aminocarbonylmethylsulfanyl)-6-benzylsulfanyl-pyrimidine-5-carbonitrile (2c). Compound **2c** was obtained from compound **1b** in reaction with chloroacetic acid amide in 43% yield (0.81 g); mp: 239-241 °C; ir: 2976, 2925, 2213, 1673 cm^{-1}; ^{1}H nmr (DMSO-d6): δ 3.92 (s, 2H, -SC*H*$_2$CO-), 3.99 (s, 2H, -COC*H*$_2$S-), 4.55 (s, 2H, -SC*H*$_2$C$_6$H$_5$), 7.26-7,61 (m, 5H, phenyl protons); ms: m/z 405 (M$^+$, 39%), 388 (38%), 347 (32%). *Anal.* Calcd. for $C_{16}H_{15}N_5O_2S_3$: C, 47.39; H, 3.73; N, 17.27; S, 23.72. Found: C, 47.38; H, 3.76; N, 17.30; S, 23.74.

6-Benzylsulfanyl-2,4-bis(pyrrolidinocarbonylmethylsulfanyl)pyrimidine-5-carbonitrile (2d). Compound **2d** was obtained from compound **1b** in reaction with chloroacetic acid pyrrolidide in 51% yield (1.22 g); mp: 191-194 °C; ir: 2921, 2854, 2206, 1668 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.77-2.03 (m, 8H, 2x -$CH_2(CH_2)CH_2$-), 3.33-3.62 (m, 8H, 2x -CH_2NCH_2-), 3.96 (s, 2H, -SCH_2CO-), 4.00 (s, 2H, -$COCH_2S$-), 4.43 (s, 2H, -$SCH_2C_6H_5$), 7.24-7.31 (m, 5H, phenyl protons); ms: m/z 513 (M^+, 5%). *Anal.* Calcd. for $C_{24}H_{27}N_5O_2S_3$: C, 56.11; H, 5.30; N, 13.63; S, 18.73. Found: C, 56.20; H, 5.28; N, 13.65; S, 18.93.

General Procedure for the Preparation of Aromatic Substituted 2,4-Bis-(aminocarbonylmethylsulfanyl)-6-methylsulfanylpyrimidine-5-carbonitriles (3a-c). To a suspension of 4.65 mmol (1.0 g) of compound **1a** in 30 ml dry methanol were added 9.30 mmol (0.94 g) TEA and 9.30 mmol of the respective chloroacetic acid amide. After 3-4 hours standing at room temperature the precipitate was collected by suction filtration and recrystallized from 2-methoxyethanol.

2,4-Bis(anilinocarbonylmethylsulfanyl)-6-methylsulfanylpyrimidine-5-carbonitrile (3a). Compound **3a** was obtained from compound **1a** in reaction with chloroacetic acid anilide in 62% yield (1.39 g); mp: 234-237 °C; ir: 3061, 2928, 2214, 1665 cm^{-1}; ^1H nmr (deuterio-chloroform): δ 2.57 (s, 3H, -SCH_3), 3.85 (s, 2H, -SCH_2CO-), 3.93 (s, 2H, -$COCH_2S$-), 7.12-7.60 (m, 10H, phenyl protons); ms: m/z 481 (M^+, 25%), 389 (100%), 362 (19%). *Anal.* Calcd. for $C_{22}H_{19}N_5O_2S_3$: C, 54.86; H, 3.98; N, 14.54; S, 19.97. Found: C, 54.87, H, 3.78, N; 14.33; S, 19.47. HRMS: calcd. for $C_{22}H_{19}N_5O_2S_3$ $(M+H)^+$ 481.0701, found 481.0722.

2,4-Bis[(4-methylanilino)carbonylmethylsulfanyl]-6-methylsulfanylyrimidine-5-carbonitrile (3b). Compound **3b** was obtained from compound **1a** in reaction with chloroacetic acid 4-methylanilide in 71% yield (1.68 g); mp: 157-159 °C; ir: 3037, 2928, 2829, 2213, 1660 cm^{-1}; ^1H nmr (deuterio-chloroform): δ 2.20 (s, 6H, 2x -CH_3), 2.58 (s, 3H, -SCH_3), 3.86 (s, 2H, -SCH_2CO-), 3.94 (s, 2H, -$COCH_2S$-), 6.96-7.29 (m, 8H, phenyl protons); ms: m/z 509 (M^+, 28%), 403 (100%), 376 (18%). *Anal.* Calcd. for $C_{24}H_{23}N_5O_2S_3$: C, 56.56; H, 4.55; N, 13.74; S, 18.87. Found: C, 56.83; H, 4.39; N, 14.07; S 18.41. HRMS: calcd for $C_{24}H_{23}N_5O_2S_3$ $(M+H)^+$ 509.1014, found 509.1029.

2,4-Bis[(4-methoxyanilino)carbonylmethylsulfanyl]-6-methylsulfanylpyrimidine-5-carbonitrile (3c). Compound **3c** was obtained from compound **1a** in reaction with chloroacetic acid 4-methoxyanilide in 80% yield (2.01 g); mp: 254-256 °C; ir: 3070, 3003, 2933, 2835, 2214, 1664 cm^{-1}; ^1H nmr (deuterio-chloroform): δ 2.58 (s, 3H, -SCH_3), 3.77 (s, 6H, 2X -OCH_3), 3.88 (s, 2H, -SCH_2CO-), 3.91 (s, 2H, -$COCH_2S$-), 6.83-7.48 (m, 8H, phenyl protons); ms: m/z 541 (M^+, 25%), 419 (55%), 392 (4%). *Anal.* Calcd. for $C_{24}H_{23}N_5O_4S_3$: C, 53.22; H, 4.28; N, 12.93; S, 17.76. Found: C, 53.42; H, 4.22; N, 13.05; S, 18.26. HRMS: calcd. for $C_{24}H_{23}N_5O_4S_3$ $(M+H)^+$ 541.0912, found 541.0935.

General Procedure for the Preparation of Aromatic Substituted 2,4-Bis-(aminocarbonylmethylsulfanyl)-6-benzylsulfanylpyrimidine-5-carbonitriles (3d-f). Compound **1b** (3.44 mmol, 1.0 g) was suspended in 30 ml dry methanol. After addition of 6.88 mmol (0.69 g) TEA and 6.9 mmol of the respective chloroacetic acid amide the reaction was allowed to stand for 3-4 hours. After that time the precipitate was collected by suction filtration and recrystallized from 2-methoxyethanol.

2,4-Bis(anilinocarbonylmethylsulfanyl)-6-benzylsulfanylpyrimidine-5-carbonitrile (3d). Compound **3d** was obtained from compound **1b** in reaction with chloroacetic acid anilide in 53% yield (1.02 g); mp: 228-230 °C; ir: 3061, 2985, 2918, 2211, 1658 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.85 (s, 2H, -SCH_2CO-), 3.91 (s, 2H, -$COCH_2S$-), 4.42 (s, 2H, -$SCH_2C_6H_5$), 7.13-7.59 (m, 15H, phenyl protons); ms: m/z 557 (M^+, 7%), 465 (18%), 438 (4%). *Anal.* Calcd. for $C_{28}H_{23}N_5O_2S_3$: C, 60.30; H, 4.16; N, 12.56; S, 17.25. Found: C, 60.21; H, 4.07; N, 12.66; S, 16.98.

6-Benzylsulfanyl-2,4-bis[(4-methylanilino)carbonylmethylsulfanyl]pyrimidine-5-carbonitrile (3e). Compound **3e** was obtained from compound **1b** in reaction with chloroacetic acid 4-methylanilide in 56% yield (1.13 g); mp: 231-233 °C; ir: 2921, 2214, 1660 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.24 (s, 6H, 2x -$C_6H_4CH_3$), 3.88 (s, 2H, -SCH_2CO-), 3.93 (s, 2H, -$COCH_2S$-), 4.38 (s, 2H, -$SCH_2C_6H_5$), 7.03-7.38 (m, 13H, phenyl protons); ms: m/z 585 (M^+, 7%), 479 (21%), 452 (6%). *Anal.* Calcd. for $C_{30}H_{27}N_5O_2S_3$: C, 61.51; H, 4.65; N, 11.96; S, 16.42. Found: C, 61.25; H, 4.58; N, 12.06; S, 16.34.

6-Benzylsulfanyl-2,4-bis[(4-methoxyanilino)carbonylmethylsulfanyl]pyrimidine-5-carbonitrile (3f). Compound **3f** was obtained from compound **1b** in reaction with chloroacetic acid 4-methoxyanilide in 59% yield(1.25 g); mp: 241-243 °C; ir: 2924, 2857, 2207, 1655 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.68 (s, 6H, 2x -OCH_3), 3.83 (s, 2H, -SCH_2CO-), 3.88 (s, 2H, -$COCH_2S$-), 4.34 (s, 2H, -$SCH_2C_6H_5$), 6.72-7.35 (m, 13H, phenyl protons); ms: m/z 617 (M^+, 2%), 495 (4%). *Anal.* Calcd. for $C_{30}H_{27}N_5O_4S_3$: C, 58.33; H, 4.41; N, 11.34, S, 15.57. Found: C, 58.33; H, 4.34; N, 11.23; S, 15.34.

General Procedure for the Reaction of the Bisalkylated Compounds with Various Secondary Amines. The respective bisalkylated compound (**2a**-**d**, **3d**-**f**) (0.1 g) were suspended in 10 ml 2-methoxyethanol. After adding 0.1 g of the corresponding secondary amine the reaction was stirred at room temperature for 3 hours in the case of pyrrolidine or piperidine and 30 hours in case the of morpholine. After addition of 30 ml water the precipitate was filtered of and recrystallized from 2-methoxyethanol.

4-(Aminocarbonylmethylsulfanyl)-6-methylsulfanyl-2-pyrrolidinopyrimidine-5-carbonitrile (4a). Compound **4a** was obtained from compound **2a** and pyrrolidine in 46% yield (43 mg); mp: 263-265 °C; ir: 2930, 2875, 2203, 1674 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 1.98-2.00 (m, 4H, -$CH_2(CH_2)_2CH_2$-), 2.52 (s, 3H, -SCH_3), 3.61-3.64 (m, 4H, -CH_2NCH_2-), 3.79 (s, 2H, -SCH_2CO-); ms: m/z 309 (M^+, 33%), 265 (14%), 251 (100%). *Anal.* Calcd. for $C_{12}H_{15}N_5OS_2$: C, 46.58; H, 4.89; N, 22.63; S, 20.73. Found: C, 46.53; H, 5.01; N, 22.19; S, 20.18. HRMS: calcd. for $C_{12}H_{15}N_5OS_2$ $(M+H)^+$ 309.0718, found 309.0718.

4-(Aminocarbonylmethylsulfanyl)-6-methylsulfanyl-2-piperidinopyrimidine-5-carbonitrile (4b). Compound **4b** was obtained from compound **2a** and piperidine in 49% yield (48 mg); mp: 231-233 °C; ir: 2937, 2856, 2202, 1668 cm^{-1}; ^1H nmr (deuterio-chloroform/methanol-d4): δ 1.68-1.69 (m, 6H, -$CH_2(CH_2)_3CH_2$-), 2.51 (s, 3H, -SCH_3), 3.75 (s, 2H, -SCH_2CO-), 3.82-3.86 (m, 4H, -CH_2NCH_2-); ms: m/z 323 (M^+, 29%), 279 (9%), 265 (100%). *Anal.* Calcd. for $C_{13}H_{17}N_5OS_2$: C, 48.27; H, 5.30; N, 21.65; S, 19.83. Found: C, 48.27; H, 5.21; N, 20.98; S, 19.67. HRMS: calcd. for $C_{13}H_{17}N_5OS_2$ $(M+H)^+$ 323.0875, found 323.0870.

4-(Aminocarbonylmethylsulfanyl)-6-methylsulfanyl-2-morpholinopyrimidine-5-carbonitrile (4c). Compound **4c** was obtained from compound **2a** and morpholine in 45% yield (44 mg); mp: 262-264 °C; ir: 2927, 2857, 2205, 1674 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 2.51 (s, 3H, -SCH_3), 3.73-3.75 (m, 4H, -CH_2NCH_2-), 3.76 (s, 2H, -SCH_2CO-), 3.86-3.91 (m, 4H, -CH_2OCH_2-); ms: m/z 325 (M^+, 43%), 281 (11%), 267 (100%). *Anal.* Calcd. for $C_{12}H_{15}N_5O_2S_2$: C, 44.29; H, 4.65; N, 21.52; S, 19.71. Found: C, 44.36; H, 4.66; N, 21.11; S, 20.10.

6-Methylsulfanyl-4-(pyrrolidinocarbonylmethylsulfanyl)-2-pyrrolidinopyrimidine-5-carbonitrile (4d). Compound **4d** was obtained from compound **2b** and pyrrolidine in 51% yield (42 mg); mp: 210-213 °C; ir: 2926, 2876, 2200, 1648 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.82-2.01 (m, 8H, 2x -CH_2(CH_2)$_2$CH_2-), 2.51 (s, 3H, -SCH_3), 3.46-3.64 (m,8H, 2x -CH_2NCH_2-), 3.99 (s, 2H, -SCH_2CO-); ms: m/z 363 (M^+, 54%), 293 (7%), 265 (9%), 251 (100%). *Anal.* Calcd. for $C_{16}H_{21}N_5OS_2$: C, 52.87; H, 5.82; N, 19.27; S, 17.64. Found: C, 53.12; H, 5.81; N, 19.20; S, 17.72.

6-Methylsulfanyl-4-(pyrrolidinocarbonylmethylsulfanyl)-2-piperidinopyrimidine-5-carbonitrile (4e). Compound **4e** was obtained from compound **2b** and piperidine in 44% yield (38 mg); mp: 179-182 °C; ir: 2934, 2871, 2203, 1644 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55-1.69 (m, 6H, -CH_2(CH_2)$_3$CH_2-), 1.84-1.99 (m, 4H, -CH_2(CH_2)$_2$CH_2-), 2.49 (s, 3H, -SCH_3), 3.46-3.53 (m, 4H, -CH_2NCH_2- from pyrrolidine), 3.82 (m, 4H, -CH_2NCH_2- from piperidine), 3.94 (s, 2H, -SCH_2CO-); ms: m/z 377 (M^+, 38%), 307 (5%), 279 (7%), 265 (100%). *Anal.* Calcd. for $C_{17}H_{23}N_5OS_2$: C, 54.08; H, 6.14; N, 18.55; S, 16.99. Found: C, 54.26; H, 6.29; N, 18.67, S, 16.96.

6-Methylsulfanyl-2-morpholino-4-(pyrrolidinocarbonylmethylsulfanyl)pyrimidine-5-carbonitrile (4f). Compound **4f** was obtained from compound **2b** and morpholine in 40% yield (35 mg); mp: 186-188 °C; ir: 2920, 2861, 2209, 1668 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.83-2.01 (m, 4H, -CH_2(CH_2)$_2$-CH_2-), 2.49 (s, 3H, -SCH_3), 3.45-3.52 (m, 4H, -CH_2NCH_2- from pyrrolidine), 3.72-3.75 (m, 4H, -CH_2NCH_2- from morpholine), 3.87-3.88 (m, 4H, -CH_2OCH_2-), 3.94 (s, 2H, -SCH_2CO-); ms: m/z 379 (M^+, 57%), 309 (7%), 281 (9%), 267 (100%). *Anal.* Calcd. for $C_{16}H_{21}N_5O_2S_2$: C, 50.64; H, 5.58; N, 18.45; S, 16.90. Found: C, 50.47; H, 5.62; N, 18.01; S, 16.19. HRMS: calcd. for $C_{16}H_{21}N_5O_2S_2$ $(M+H)^+$ 379.1137, found 379.1129.

4-(Aminocarbonylmethylsulfanyl)-6-benzylsulfanyl-2-pyrrolidinopyrimidine-5-carbonitrile (5a). Compound **5a** was obtained from compound **2c** and pyrrolidine in 47% yield (45 mg); mp: 226-228 °C; ir: 3028, 2936, 2872, 2204, 1666 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95-1.98 (m, 4H, -CH_2(CH_2)$_2$-CH_2-), 3.57-3.63 (m, 4H, -CH_2NCH_2-), 3.78 (s, 2H, -SCH_2CO-), 4.41 (s, 2H, -SCH_2C$_6$H$_5$), 7.20-7.39 (m, 5H, phenyl protons); ms: m/z 385 (M^+, 100%), 341 (43%), 327 (69%). *Anal.* Calcd. for $C_{18}H_{19}N_5OS_2$: C, 56.08; H, 4.97; N, 18.17; S, 16.64. Found: C, 55.73; H, 5.05; N, 17.89; S, 16.05. HRMS: calcd. for $C_{18}H_{19}N_5OS_2$ $(M+H)^+$ 385.1031, found 385.1029.

4-(Aminocarbonylmethylsulfanyl)-6-benzylsulfanyl-2-piperidinopyrimidine-5-carbonitrile (5b). Compound **5b** was obtained from compound **2c** and piperidine in 45% yield (44 mg); mp: 228-231 °C; ir: 3028, 2931, 2854, 2204, 1664 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 1.39-1.50 (m, 6H, -CH_2(CH_2)$_3$CH_2-), 3.58 (s, 2H, -SCH_2CO-), 3.64 (m, 4H, -CH_2NCH_2-), 4.20 (s, 2H, -SCH_2C$_6$H$_5$), 7.03-7.16 (m, 5H, phenyl protons); ms: m/z 399 (100% M^+), 355 (30%), 341 (96%). *Anal.* Calcd. for $C_{19}H_{21}N_5OS_2$: C, 57.12; H, 5.30; N, 17.53; S, 16.05. Found: C, 56.79; H, 5.13; N, 17.01; S, 15.27. HRMS: calcd. for $C_{19}H_{21}N_5OS_2$ $(M+H)^+$ 399.1188, found 399.1197.

4-(Aminocarbonylmethylsulfanyl)-6-benzylsulfanyl-2-morpholinopyrimidine-5-carbonitrile (5c). Compound **5c** was obtained from compound **2c** and morpholine in 48% yield (47 mg); mp: 233-236 °C; ir: 3029, 2924, 2855, 2212, 1675 cm^{-1}; ^1H nmr (DMSO-d6): δ 3.61-3.62 (t, 4H, -CH_2NCH_2-), 3.84-3.86 (t, 4H, -CH_2OCH_2-), 3.92 (s, 2H, -SCH_2CO-), 4.54 (s, 2H, -SCH_2C$_6$H$_5$), 7.14-7.63 (m, 5H, phenyl protons); ms: m/z 401 (M^+, 96%), 394 (8%), 357 (36%), 343 (39%). *Anal.* Calcd. for $C_{18}H_{19}N_5O_2S_2$: C, 53.85; H, 4.77; N, 17.44; S, 15.97. Found: C, 54.11; H, 4.65; N, 17.52; S, 15.69.

6-Benzylsulfanyl-4-(pyrrolidinocarbonylsulfanyl)-2-pyrrolidinopyrimidine-5-carbonitrile (5d). Compound **5d** was obtained from compound **2d** an pyrrolidine in 49% yield (85 mg); mp: 191-196 °C; ir: 2873, 2200, 1645 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.83-1.99 (m, 8H, 2x -CH_2(CH_2)$_2$CH_2-), 3.45-3.62 (m, 8H, 2x -CH_2NCH_2-), 3.98 (s, 2H, -SCH_2CO-), 4.40 (s, 2H, -SCH_2C$_6$H$_5$), 7.19-7.35 (m, 5H, phenyl protons); ms: m/z 439 (M^+, 21%), 341 (6%), 327 (100%). *Anal.* Calcd. for $C_{22}H_{25}N_5OS_2$: C, 60.11; H, 5.73; N, 15.93; S, 14.59. Found: C, 59.97; H, 5.84; N, 16.48; S, 14.10. HRMS: calcd. for $C_{22}H_{25}N_5OS_2$ $(M+H)^+$ 439.1501, found 439.1501.

6-Benzylsulfanyl-2-piperidino-4-(pyrrolidinocarbonylsulfanyl)-pyrimidine-5-carbonitrile (5e). Compound **5e** was obtained from compound **2d** and piperidine in 30% yield (26 mg); mp: 155-157 °C; ir: 3061, 2937, 2870, 2202, 1645 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55-1.67 (m, 6H, -CH_2(CH_2)$_3$-CH_2-), 1.85-1.98 (m, 4H, -CH_2(CH_2)$_2$CH_2-), 3.47-3.49 (m, 4H, -CH_2NCH_2- from pyrrolidine), 3.80 (s, 4H, -CH_2NCH_2- from morpholine), 3.92 (s, 2H, -SCH_2CO-), 4.36 (s, 2H, -SCH_2C$_6$H$_5$), 7.24-7.32 (m, 5H, phenyl protons); ms: m/z 453 (M^+, 16%), 362 (15%), 355 (6%). *Anal.* Calcd. for $C_{23}H_{27}N_5OS_2$: C, 60.90; H, 6.00; N, 15.44; S, 14.14. Found: C, 60.45; H, 5.94; N, 15.43; S, 14.11. HRMS: calcd. for $C_{23}H_{27}N_5OS_2$ $(M+H)^+$ 453.1657, found 453.1664.

4-(Anilinocarbonylmethylsulfanyl)-6-benzylsulfanyl-2-morpholinopyrimidine-5-carbonitrile (6a). Compound **6a** was obtained from compound **3d** and morpholine in 44% yield (38 mg); mp: 248-250 °C; ir: 3061, 2921, 2857, 2206, 1665 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.61 (m, 4H, -CH_2NCH_2-), 3.81-3.83 (m, 4H, -CH_2OCH_2-), 3.84 (s, 2H, -SCH_2CO-), 4.37 (s, 2H, -SCH_2C$_6$H$_5$), 7.11-7.45 (m, 10H, phenyl protons); ms: m/z 477 (M^+, 100%), 385 (16%), 358 (42%), 343 (68%). *Anal.* Calcd. for $C_{24}H_{23}N_5O_2S_2$: C, 60.36; H, 4.85; N, 14.66, S, 13.43. Found: C, 60.52; H, 4.92; N, 14.63; S, 13.25.

6-Benzylsulfanyl-4-[(4-methylanilino)carbonylmethylsulfanyl]-2-morpholinopyrimidine-5-carbonitrile (6b). Compound **6b** was obtained from compound **3e** and morpholine in 46% yield (39 mg); mp: 250-253 °C; ir: 3030, 2916, 2858, 2205, 1669 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.29 (s, 3H, -CH_3), 3.60 (m, 4H, -CH_2NCH_2-), 3.81-3.82 (m, 4H, -CH_2OCH_2-), 3.83 (s, 2H, -SCH_2CO-), 4.37 (s, 2H, -SCH_2C$_6$H$_5$), 7.09-7.33 (m, 9H, phenyl protons); ms: m/z 491 (M+, 63%), 385 (33%), 358 (100%), 343 (43%). *Anal.* Calcd. for $C_{25}H_{25}N_5O_2S_2$: C, 61.08; H, 5.13; N, 14.25; S, 13.04. Found: C, 61.13; H, 5.14; N, 14.01; S, 12.54. HRMS: calcd. for $C_{25}H_{25}N_5O_2S_2$ $(M+H)^+$ 491.1450, found 491.1465.

6-Benzylsulfanyl-4-[(4-methoxyanilino)carbonylmethylsulfanyl]-2-morpholinopyrimidine-5-carbonitrile (6c). Compound **6c** was obtained from compound **3f** and morpholine in 43%

yield (35 mg); mp: 251-253 °C; ir: 2923, 2856, 2207, 1656 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.62 (m, 4H, -CH_2NCH_2-), 3.76 (s, 3H, -OCH_3), 3.81-3.83 (m, 4H, -CH_2OCH_2-), 3.84 (s, 2H, -SCH_2CO-), 4.37 (s, 2H, -SC$H_2C_6H_5$), 6.82-7.34 (s, 9H, phenyl protons); ms: m/z 507 (M^+, 55%), 385 (36%), 358 (100%), 343 (19%). *Anal.* Calcd. for $C_{25}H_{25}N_5O_3S_2$: C, 59.15; H, 4.96; N, 13.80; S, 12.63. Found: C, 59.42; H, 5.04; N, 13.71; S, 12.38.

General Procedure for the Cyclization to Thieno[2,3-*d*]-pyrimidines. The respective 6-Alkylsulfanyl-2-*sec*-amino-4-aminocarbonylmethylsulfanylpyrimidin-5-carbonitrile (100 mg) were suspended in 10 ml of 2-methoxyethanol. After addition of 1-2 drops of a 5 *M* solution of sodium methoxide the suspension was stirred at room temperature. After 1-3 hours the reaction was cooled down and 30 ml water were added. The resulting yellow precipitate was extracted three times with 15 ml chloroform. The organic layer was dried over sodium sulfate and the solvent was removed under vacuum. The resulting residue was purified by recrystallization from a small amount of 2-methoxyethanol.

5-Amino-4-methylsulfanyl-2-pyrrolidinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Amide (7a). Compound **7a** was obtained from compound **4a** in 42% yield (42 mg); mp: 229-231 °C; ir: 2971, 2872, 1646 cm^{-1}, ^1H nmr (deuteriochloroform/methanol-d4): δ 1.97-2.00 (m, 4H, -CH_2(CH_2)$_2$CH_2-), 2.66 (s, 3H, -SCH_3), 3.61-3.70 (m, 4H, -CH_2NCH_2-); ms: m/z 323 (M^+, 100%), 306 (10%), 278 (11%). *Anal.* Calcd. for $C_{12}H_{15}N_5OS_2$: C, 46.58; H, 4.89; N, 22.63; S, 20.73. Found: C, 46.30; H, 4.92; N, 22.47; S, 20.84.

5-Amino-4-methylsulfanyl-2-piperidinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Amide (7b). Compound **7b** was obtained from compound **4b** in 45% yield (45 mg); mp: 203-205 °C; ir: 2928, 2852, 1646 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 1.59-1.68 (m, 6H, -CH_2(CH_2)$_3$CH_2-), 2.64 (s, 3H, -SCH_3), 3.83-3.86 (t, 4H, -CH_2NCH_2-); ms: m/z 323 (M^+, 100%), 306 (10%), 278 (11%). *Anal.* Calcd. for $C_{13}H_{17}N_5OS_2$: C, 48.27; H, 5.30; N, 21.65; S, 19.83. Found: C, 48.15; H, 5.27; N, 21.02; S, 19.39. HRMS: calcd. for $C_{13}H_{17}N_5OS_2$ $(M+H)^+$ 323.0875, found 323.0882.

5-Amino-4-methylsulfanyl-2-morpholinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Amide (7c). Compound **7c** was obtained from compound **4c** in 40% yield (40 mg); mp: 232-235 °C; ir: 2923, 2854, 1638 cm^{-1}, ^1H nmr (deuteriochloroform/methanol-d4): δ 2.64 (s, 3H, -SCH_3), 3.75-3.77 (t, 4H, -CH_2NCH_2-), 3.87-3.89 (t, 4H, -CH_2OCH_2-); ms: m/z 325 (M^+, 100%), 308 (7%), 280 (9%). *Anal.* Calcd. for $C_{12}H_{15}N_5O_2S_2$: C, 44.29; H, 4.65; N, 21.53; S, 19.71. Found: C, 43.87; H, 4.61; N, 21.31; S, 19.54. HRMS: calcd. for $C_{12}H_{15}N_5O_2S_2$ $(M+H)^+$ 325.0667, found 325.0675.

5-Amino-4-methylsulfanyl-2-pyrrolidinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Pyrrolidide (7d). Compound **7d** was obtained from compound **4d** in 39% yield (39 mg); mp: 199-202 °C; ir: 2969, 2874, 1636 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.84-1.99 (m, 8H, -CH_2(CH_2)$_2$CH_2-), 2.65 (s, 3H -SCH_3), 3.46-3.68 (m, 8H, -CH_2NCH_2-); ms: m/z 363 (M^+, 64%), 293 (41%), 266 (40%). *Anal.* Calcd. for $C_{16}H_{21}N_5OS_2$: C, 52.87; N, 5.82; H, 19.27; S, 17.64. Found: C, 52.75; H, 5.58; N, 19.04; S, 17.52.

5-Amino-4-methylsulfanyl-2-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylic Acid Pyrrolidide (7e). Compound **7e** was obtained from compound **4e** in 42% yield (42 mg); mp: 230-233 °C; ir: 2939, 2854 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55-1.67 (m, 6H, -CH_2(CH_2)$_3$CH_2-), 1.89-1.93 (m, 4H, -CH_2(CH_2)$_2$CH_2-), 2.63 (s, 3H -SCH_3), 3.66-3.85 (m, 8H, 2x -CH_2NCH_2-); ms: m/z 377 (M^+, 100%), 307 (75%), 280 (88%). *Anal.* Calcd. for $C_{17}H_{23}N_5OS_2$: C, 54.08; H, 6.14; N, 18.55; S, 16.99. Found: C, 53.79; H, 5.76; N, 18.41; S, 16.98.

5-Amino-4-benzylsulfanyl-2-pyrrolidinothieno[2,3-*d*]pyrimidine-6-carboxylic Acid Amide (7f). Compound **7f** was obtained from compound **5a** in 39% yield (39 mg); mp: 202-204 °C; ir: 2968, 2871, 1640 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): 1.98-2.03 (m, 4H, -CH_2(CH_2)$_2$-CH_2-), 3.57-3.69 (m, 4H, -CH_2NCH_2-), 4.61 (s, 2H, -SC$H_2C_6H_5$), 7.08-7.39 (m, 5H, phenyl protons); ms: m/z 385 (M^+, 100%), 368 (37%), 340 (18%). *Anal.* Calcd. for $C_{18}H_{19}N_5OS_2$: C, 56.08; H, 4.97; N, 18.17; S, 16.64. Found: C, 55.74; H, 4.92; N, 17.64; S, 16.35. HRMS: calcd. for $C_{18}H_{19}N_5OS_2$ $(M+H)^+$ 385.1031, found 385.1020.

5-Amino-4-benzylsulfanyl-2-piperidinothieno[2,3-*d*]pyrimidine-6-carboxylic Acid Amide (7g). Compound **7g** was obtained from compound **5b** in 41% yield (41 mg); mp: 223-226 °C; ir: 2930, 2851, 1644 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 1.54-1.67 (m, 6H, -CH_2(CH_2)$_3$-CH_2-), 3.79-3.87 (m, 4H, -CH_2NCH_2-), 4.56 (s, 2H, -SC$H_2C_6H_5$), 7.24-7.41 (m, 5H, phenyl protons); ms: m/z 399 (M^+, 100%), 382 (26%), 354 (9%), 308 (16%). *Anal.* Calcd. for $C_{19}H_{21}N_5OS_2$: C, 57.12; H, 5.30; N, 17.53; S, 16.05. Found: C, 56.92; H, 5.25; N, 17.45; S, 15.83.

5-Amino-4-benzylsulfanyl-2-morpholinothieno-[2,3-*d*]-pyrimidine-6-carboxylic Acid Amide (7h). Compound **7h** was obtained from compound **5c** in 37% yield (37 mg); mp: 207-210 °C; ir: 2914, 2854, 1644 cm^{-1}; ^1H nmr (deuteriochloroform/methanol-d4): δ 3.71-3.74 (m, 4H, -CH_2NCH_2-), 3.83-3.87 (m, 4H, -CH_2OCH_2-), 4.55 (s, 2H, -SC$H_2C_6H_5$), 7.23-7.37 (m, 5H, phenyl protons); ms: m/z 401 (M^+, 100%), 384 (23%), 358 (22%). *Anal.* Calcd. for $C_{18}H_{19}N_5O_2S_2$: C, 53.85; H, 4.77; N, 17.44; S, 15.97. Found: C; 53.41; H, 4.76; N, 17.08; S, 15.39. HRMS: calcd. for $C_{18}H_{19}N_5O_2S_2$ $(M+H)^+$ 401.0980, found 401.0983.

5-Amino-4-benzylsulfanyl-2-pyrrolidinothieno[2,3-*d*]-pyrimidine-6-carboxylic Acid Pyrrolidide (7i). Compound **7i** was obtained from compound **5d** in 35% yield (35 mg); mp: 197-201 °C; ir: 2968, 2872, 1634 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.84-1.99 (m, 8H, -CH_2(CH_2)$_2$CH_2-), 3.46-3.69 (m, 8H, -CH_2NCH_2-), 4.41 (s, 2H, -SC$H_2C_6H_5$), 7.19-7.41 (m, 5H, phenyl protons); ms: m/z 439 (M^+, 100%), 369 (41%), 342 (34%). *Anal.* Calcd. for $C_{22}H_{25}N_5OS_2$: C, 61.08; H, 5.13; N, 14.25; S, 13.04. Found: C, 60.93; H 5.16; N, 14.13; S, 12.89.

5-Amino-4-benzylsulfanyl-2-morholinothieno[2,3-*d*]pyrimidine-6-carboxylic Acid Anilide (7j). Compound **7j** was obtained from compound **6a** in 46% yield (46 mg); mp: 205-207 °C; ir: 3028, 2921, 2855, 1637 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.73-3.76 (t, 4H -CH_2NCH_2-), 3.86-3.89 (t, 4H, -CH_2OCH_2-), 4.57 (s, 2H, -SC$H_2C_6H_5$), 7.07-7.51 (m, 10H, phenyl protons); ms: m/z 477 (M+, 76%), 385 (100%), 358 (18%). *Anal.* Calcd. for $C_{24}H_{23}N_5O_2S_2$: C, 60.36; H, 4.85; N, 14.66; S, 13.43. Found: C, 59.82; H 4.83; N, 14.49; S, 13.16. HRMS: calcd. for $C_{24}H_{23}N_5O_2S_2$ $(M+H)^+$ 477.1293, found 477.1291.

5-Amino-4-benzylsulfanyl-2-morholinothieno[2,3-*d*]pyrimidine-6-carboxylic Acid 4-Methylanilide (7k). Compound **7k** was obtained from compound **6b** in 42% yield (42 mg); mp: 231-233 C; ir: 3028, 2918, 2856, 1632 cm^{-1}; ^1H nmr

(deuteriochloroform): δ 2.31 (s, 3H, -CH_3), 3.73-3.75 (t, 4H -CH_2NCH_2-), 3.86-3.88 (t, 4H, -CH_2OCH_2-), 4.56 (s, 2H, -SCH_2C$_6$H$_5$), 7.11-7.39 (m, 9H, phenyl protons); ms: m/z 491 (M^+, 86%), 385 (100%), 358 (23%). *Anal.* Calcd. for $C_{25}H_{25}N_5O_2S_2$: C, 61.08; H, 5.13; N, 14.25; S, 13.04. Found: C, 60.93; H 5.16; N, 14.13; S, 12.89.

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