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Synthesis and Reactions of New 4-Chloro-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]-benzimidazoles

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Summary. 4-Chloro-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole (**3**) was prepared by chlorination of **2** which could also be converted directly to 2-methylpyrimidino[4′,5′:4,5]-thiazolo[3,2-*a*]benzimidazol-4-thiol (**4**). Nucleophilic substitution of **3** with alcohols, phenols, primary amines, secondary amines, sodium azide, and mercaptoacetic acid gave the corresponding derivatives. The thiol derivative **4** was reacted with alkyl/aralkyl halides, phenacyl bromide derivatives, bromoacetone, chloroanilides, bromomalonic ester, and ethyl bromoacetate to afford compounds of potential pharmacological interest.

Keywords. Pyrimidothiazolobenzimidazole; Chlorination; Nucleophilic substitution; Condensation; Pharmacological interest.

Synthese und Reaktionen neuer 4-Chlor-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole

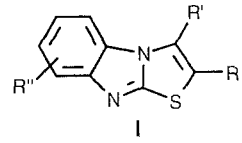
Zusammenfassung. 4-Chlor-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol (**3**) wurde durch Chlorierung von **2**, welches auch direkt zu 2-Methylpyrimidino[4′,5′:5,4]thiazolo[3,2-*a*]-benzimidazol-4-thiol (**4**) umgesetzt werden kann, hergestellt. Nucleophile Substitution von **3** mit Alkoholen, Phenolen, primären Aminen, sekundären Aminen, Natriumazid und Mercaptoessigsäure ergab die entsprechenden Derivate. Das Thiolderivat **4** wurde mit Alkyl/Alkarylhalogeniden, Phenacylbromidderivaten, Bromaceton, Chloraniliden, Brommalonsäureester und Bromessigsäure-ethylester zu potentiell pharmakologisch interessanten Verbindungen umgesetzt.

Introduction

Thiazolo[3,2-*a*]benzimidazole derivatives (**I**) exhibit antibacterial activity [1] and act as hypoglycemic agents [2]. They are associated with a particularly wide range of biological properties including antitumor [3, 4], antiviral [5], and antitubercular [6] activity, as well as with a depressant effect on the central nervous system [6, 7], anticonvulsant [8–10], antispasmodic [8, 9], and hypotensive activity [11, 12].

In addition, fungicidal [1, 13–16], herbicidal [17], insecticidal [16], and plant growth regulating properties have been reported [18]. They have been employed as a chromophoric unit in cyanine dyes [19, 20, 21] and as photographic sensitizing

agents [22–24]. Numerous studies have been reported which show their antitumor and antimetastatic activity [25, 26].

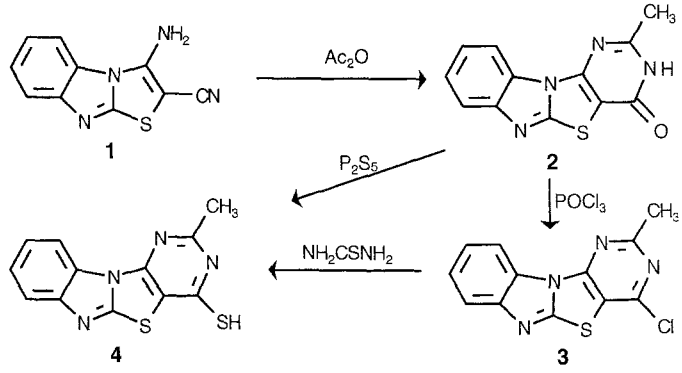


I

Recently, the synthesis and properties of derivatives of **I** with pyrimido heterocycles fused at positions R,R' have been reported [27–30]. Their synthetic aspects with respect to the generation of potential pharmacologically interest will be now reported.

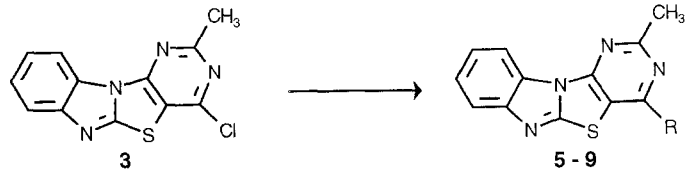
Results and Discussion

First of all, 2-methyl-3*H*-pyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol-4-one (**2**) was prepared by cyclization of 3-aminothiazolo[3,2-*a*]benzimidazol-2-carbonitrile (**1**) as recently reported [27–29]. It was chlorinated with $POCl_3$ to give silvery crystals of 4-chloro-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole (**3**) in 56% yield. Nucleophilic substitution of the chloro derivative **3** with thiourea in ethanol gave the corresponding thiol derivative **4** as white crystals in 62% yield. The thiol compound **4** which could alternatively be obtained *via* direct condensation of **2** with P_2S_5 in refluxing pyridine in 77% yield (Scheme 1).



Scheme 1

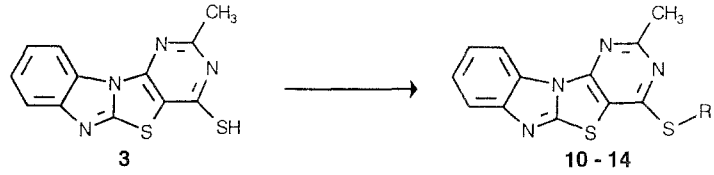
A series of chemical reactions were carried out on both the chloro compound **3** and the thiol derivative **4** (Scheme 2).



Scheme 2. **5a**: $R = CH_3$, **b**: $R = C_2H_5$, **c**: $R = p\text{-}C_6H_4CH_3$; **6a**: $R = NHCH_3$, **b**: $R = NHPh$, **c**: $R = NHNHPh$; **7a**: $R =$ morpholino, **b**: $R =$ piperidino, **c**: $R =$ N-methylpiperazino, **d**: $R =$ piperazino; **8**: $R = N_3$; **9**: $R = SCH_2COOH$

The chloro compound **3** was substituted with alcohols or *p*-cresol in presence of sodium metal giving the alkoxy/aryloxy derivatives **5a–c**. Condensation of **3** with methyl amine, aniline and or phenyl hydrazine afforded the corresponding alkyl/aryl amino derivatives **6a–c**. Furthermore, condensation of **3** with piperidine, morpholine, N-methylpiperazine, and piperazine gave the corresponding compounds **7a–d**. Treatment of **3** with sodium azide in refluxing ethanol afforded the azide derivative **8** in 65% yield rather than the cyclized form. Interaction of **3** with thioglycolic acid gave 2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol-4-thioacetic acid (**9**) in 58% yield. **9** could also be obtained from the reaction of the thiol derivative **4** with bromoacetic acid. Nucleophilic substitution of 4-chloro-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole (**3**) with KCN in ethanol gave 4-ethoxy-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole (**5b**) rather than the 4-cyano derivative because of solvolysis.

Interaction of 2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazole-4-thiol (**4**) with alkyl/aralkyl halides gave colorless crystals of 4-alkyl/aralkylthio-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazoles **10a–c** (Scheme 3).



Scheme 3. 10a: $R = CH_3$, **b**: $R = C_2H_5$, **c**: $R = CH_2Ph$; **11a**: $R = CH_2COCH_3$, **b**: $R = p$-$CH_2COC_6H_4Cl$, **c**: $R = p$-$CH_2COC_6H_4Br$; **12a**: $R = p$-$CH_2CONHC_6H_4Me$, **b**: $R = p$-$CH_2CONHC_6H_4OMe$, **c**: $R = p$-$CH_2CONHC_6H_4Br$; **13**: $R = CH_2COOC_2H_5$; **14**: $R = CH(COOC_2H_5)_2$

Reaction of **4** with bromoacetone and phenacylbromide derivatives afforded the corresponding 2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol-4-thioketones **11a–c** as colorless crystals. On the other hand, upon stirring of the thiol **4** with chloroanilide derivatives in ethanol containing KOH at room temperature, the expected thioanilides **12a–c** were obtained as white crystals. Nucleophilic reaction of thiol **4** with ethyl chloroacetate or bromomalonic ester in refluxing acetone containing K_2CO_3 gave colorless crystals of the corresponding thioesters **13** and **14**. The structures of all new compounds were confirmed by elemental analyses and spectroscopic techniques (IR, NMR, and MS).

Experimental

All melting points are uncorrected (Kofler apparatus). IR spectra were measured on a Perkin-Elmer FT spectrometer 1710 (KBr pellets). NMR spectra were recorded on a Varian EM-390 NMR spectrometer (90 MHz; Spectroscopic Unit, Assiut University, Egypt) and on WP 200 SY and AM 300 spectrometers (Bruker). *TMS* was used as an internal standard. MS spectra were obtained with a MAT 312 Mass Spectrometer (Finigan) at an ionization energy of 70 eV (Spectroscopic Unit, Hannover University, Hannover, Germany). Elemental analyses were accomplished at the microanalytical laboratory of the Chemistry Department (Assiut University, Egypt). They were found to agree satisfactorily with the calculated values. 3-Aminothiazolo[3,2-*a*]benzimidazol-2-

carbonitrile (**1**) and 2-methyl-3*H*-pyrimidino[4′,5′:4,5]thiazolo[3,2-*a*]benzimidazol-4-one (**2**) were prepared according to Refs. [27–30].

4-Chloro-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazole (**3**; $C_{12}H_7N_4ClS$)

A sample of **2** (7.68 g, 30 mmol) was refluxed in $POCl_3$ (20 ml) on a hot plate for 2 hours. The reaction mixture was cooled and diluted with ice cooled water. The resulting precipitate was collected by filtration and recrystallized from chloroform to give **3** in 56% yield.

M.p.: 205°C; IR (KBr); ν = 1610w, 1580m, 1530s, 1510s, 1500s, 1460s, 1230s, 1185s, 1025s, 750s, 730s cm^{-1}; ^1H NMR (*DMSO*-d_6, 90 MHz): δ = 2.9 (s, 3H, CH_3), 7.6–7.9 (m, 3H, arom-H), 8.5 (m, 1H, arom-H) ppm; MS: *m/z* (%) = 276 [M +1] (32), 275 [M^+] (16), 274 (100), 239 (11), 212 (4), 199 (7), 163 (2), 154 (6), 137 (8), 120 (9), 102 (7), 90 (12), 86 (15), 78 (14), 77 (7), 70 (26), 63 (4), 50 (5).

2-Methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazol-4-thiol (**4**; $C_{12}H_8N_4S_2$)

Method A. A mixture of the chloro compound **3** (8.22 g, 30 mmol) and thiourea (5.0 g, 65 mmol) was refluxed in ethanol (100 ml) for 3 h. The reaction mixture was concentrated, cooled, diluted with water, filtered off, and acidified with dilute HCl to give a pale yellow precipitate of the thiol derivative **4**. The crude product formed was further purified by crystallization from dioxane to give white crystals of the corresponding thiol derivative **4** in 62% yield; m.p.: 340–343°C.

Method B. A mixture of pyrimidin-4-one derivative **2** (2.56 g, 10 mmol) and P_2S_5 (3.0 g) was refluxed in pyridine for 5 h. The reaction mixture was cooled, filtered, and diluted with acetic acid. The resulting precipitate was collected by filtration and crystallized from dioxane to give the thiol derivative **4** in 77% yield.

IR (KBr): ν = 3145m, 2990w, 2980w, 1615w, 1580s, 1565s, 1505s, 1495s, 1460w, 1420m, 1240m, 1220m, 1210m, 1005w, 760m, 750m cm^{-1}; ^1H NMR (*TFA*, 90 MHz): δ = 2.9 (s, 3H, CH_3), 7.6–7.9 (m, 3H, arom-H), 8.5 (m, 1H, arom-H) ppm; MS: *m/z* (%) = 272 [M^+] (100), 256 (5), 239 (5), 230 (2), 214 (2), 199 (2), 186 (2), 161 (4), 155 (4), 149 (11), 136 (12), 70 (3), 57 (2).

4-Alkoxy/aryloxy-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazoles (**5a–c**)

A mixture of the chloro compound **3** (1.0 g, 3.6 mmol) and sodium metal was stirred at 50–60°C in alcohol or *p*-cresol for 2 ~ 3 h. The reaction mixture was cooled, and the resulting precipitate was collected by filtration, washed with water, and crystallized from methanol or ethanol to give the corresponding alkoxy/aryloxy derivatives **5a–c** in variant yield.

5a ($C_{13}H_{10}N_4OS$): $R = CH_3$; 78%; m.p.: 196°C; IR (KBr): ν = 3076m, 3052m, 3000m, 2952m, 2924m, 2852m, 1620m, 1572s, 1508s, 1468s, 1408s, 1372s, 1304s, 1244s, 1148s, 1108s, 1024s, 768s, 736s, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.55 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 7.3–7.8 (m, 3H, arom-H), 8.3 (m, 1H, arom-H) ppm; MS: *m/z* (%) = 270 [M^+] (100), 256 (9), 241 (19), 228 (2), 199 (10), 186 (3), 174 (3), 160 (4), 154 (3), 149 (3), 139 (2), 111 (7), 102 (5), 90 (6), 76 (2), 70 (10).

5b ($C_{14}H_{12}N_4OS$): $R = CH_2CH_3$; 88%; m.p.: 165°C IR (KBr): ν = 3030w, 2986s, 2940w, 1621w, 1573s, 1505s, 1473m, 1439s, 1406s, 1378s, 1337s, 1253m, 1135s, 1022s, 770s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.55 (t, J = 7 Hz, 3H, CH_2), 2.68 (s, 3H, CH_3), 4.55 (t, J = 7 Hz, 3H, CH_3), 7.35 (m, 2H, arom-H), 7.7 (m, 1H, arom-H), 8.16 (m, 1H, arom-H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 14.63 (CH_3), 25.87 (CH_3), 63.99 (CH_2), 101.99 (C-2), 112.99, 119.42, 122.72, 124.74 (C-7, C-8, C-9, C-10), 129.93, 148.35, 152.20, 153.04, 157.35, 165.07 (C-4a, C-11a, C-6a, C-10a, C-5a, C-4) ppm; MS: *m/z* (%) = 285 [M^+ + 1] (82), 284 [M^+] (3), 270 (17), 257 (100), 240 (4), 227 (5), 199 (4), 186 (3), 160 (10), 149 (8), 145 (8), 134 (5), 128 (6), 102 (7), 90 (8), 77 (2), 70 (12), 63 (2), 51 (2).

5c ($C_{19}H_{14}N_4OS$): $R = p\text{-}C_6H_4CH_3$; 48%; m.p.: 190°C; IR (KBr): ν = 3020w, 2960w, 1610w, 1560s, 1490m, 1460s, 1430s, 1370s, 1240s, 1095s, 1010s, 760s, 730s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): $\delta = 2.4$ (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 7.1–8.3 (m, 8H, arom-H) ppm; MS: m/z = 347 [M +1] (26), 346 [M^+] (100), 303 (4), 239 (4), 199 (1), 166 (5), 109 (5), 91 (6), 83 (4), 69 (4), 55 (4).

4-Alkyl/arylamino/phenylhydrazino-2-methylpyrimidino[4',5':4,5]thiazolo[3,2-a]benzimidazoles (**6a–c**)

A mixture of chloro compound **3** (1.0 g, 3.6 mmol) and methyl amine (3.0 ml), aniline (0.5 ml), or phenyl hydrazine (0.2 ml) in ethanol (20 ml) was heated at *ca.* 80–90°C for about 3–5 h. The precipitate resulting after cooling was collected by filtration and crystallized from dioxane or pyridine (**6c**) to give **6a–c** in good yields.

6a ($C_{13}H_{11}N_5S$): R = $NHCH_3$; 72%; m.p.: 328°C; IR (KBr): ν = 3015w, 2985w, 1600s, 1570m, 1505m, 1460m, 1260m, 1115s, 765s, 740s cm^{-1}; ^1H NMR (*TFA*, 90 MHz): δ = 3.1 (s, 3H, CH_3), 3.5 (s, 3H, CH_3), 7.7 (m, 2H, arom-H), 8.7 (m, 1H, arom-H), 9.0 (m, 1H, arom-H) ppm; MS: m/z (%) = 269 [M^+] (100), 241 (24), 240 (23), 227 (2), 214 (2), 199 (32), 186 (2), 172 (2), 160 (3), 154 (3), 149 (3), 135 (6), 129 (5), 102 (6), 77 (2), 53 (2).

6b ($C_{18}H_{13}N_5S$): R = NHPh; 61%; m.p.: 276°C; IR (KBr): ν = 3200m, 3190m, 3000w, 2960w, 2870w, 1620m, 1590s, 1570s, 1470s, 1310s, 1270s, 1220m, 1030w, 770s, 740s cm^{-1}; ^1H NMR (*TFA*, 90 MHz): δ = 3.0 (s, 3H, CH_3), 7.4–8.5 (m, 9H, arom-H) ppm; MS: m/z (%) = 331 [M^+] (100), 330 (66), 241 (7), 240 (20), 219 (9), 166 (10), 165 (11), 149 (8), 134 (8), 122 (10), 102 (10), 88 (26), 77 (21) 70 (13), 58 (17).

6c ($C_{18}H_{14}N_6S$): R = NHNHPh; 66%; m.p.: 325°C; IR (KBr): ν = 3416w, 3312m, 3199m, 3052m, 2972w, 2912w, 1604s, 1576s, 1492s, 1432s, 1304m, 1252m, 1072m, 756s cm^{-1}; ^1H NMR (*DMSO*-d_6, 90 MHz): δ = 2.7 (s, 3H, CH_3), 7.2–8.85 (m, 9H, arom-H), 9.62 (bs, 1H, NH), 10.33 (bs, 1H, NH) ppm; MS: m/z (%) = 347 [M + 1] (100), 346 [M^+] (9), 330 (4), 313 (5), 288 (3), 272 (5), 255 (69), 240 (7), 227 (16), 214 (7), 199 (10), 187 (11), 160 (6), 150 (10), 149 (1), 134 (10), 118 (6), 102 (7), 93 (14), 77 (11), 65 (8), 57 (5), 51 (5).

2-Methyl-4-piperidino/morpholino/N-methylpiperazino/piperazinopyrimidino[4',5':4,5]thiazolo-[3,2-a]benzimidazoles (**7a–d**)

A mixture of chloro compound **3** (1.0 g, 3.6 mmol) and secondary amine (3.0 ml) was fused without solvent for about 5 min. The reaction mixture was subsequently refluxed in ethanol (20 ml) for further 2 h. The resulting precipitate was collected by filtration and crystallized from ethanol or methanol to give **7a–d** in high yields.

7a ($C_{16}H_{15}N_5OS$): R = morpholino; 81%; m.p.: 160°C; IR (KBr): ν = 2960w, 2908w, 2825m, 1616s, 1588s, 1544s, 1500s, 1460s, 1440s, 1408s, 1256s, 1032m, 764s, 740m cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.62 (s, 3H, CH_3), 3.75–3.95 (m, 8H, CH_2OCH_2 and CH_2NCH_2), 7.4 (m, 2H, arom-H), 7.8 (m, 1H, arom-H), 8.35 (m, 1H, arom-H) ppm; MS: m/z (%) = 325 [M^+] (100), 307 (10), 294 (58), 280 (21), 267 (51), 255 (24), 240 (46), 212 (9), 200 (44), 172 (11), 162 (12), 154 (14), 134 (14), 129 (16), 102 (13), 91 (9), 84 (56), 70 (27), 56 (11).

7b ($C_{17}H_{17}N_5S$): R = piperidino; 78%; m.p.: 230°C; IR (KBr): ν = 2925w, 2900m, 2815m, 1610s, 1555s, 1540s, 1490s, 1460s, 1405m, 1305s, 1250s, 1195s, 1155s, 750s, 730s, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.7 (m, 6H, $(CH_2)_3$), 2.6 (s, 3H, CH_3), 3.7 (m, 4H, CH_2NCH_2), 7.3 (m, 2H, arom-H), 7.7 (m, 1H, arom-H), 8.3 (m, 1H, arom-H) ppm; MS: m/z (%) = 323 [M^+] (93), 306 (3), 294 (34), 280 (64), 268 (100), 254 (12), 240 (48), 226 (3), 212 (7), 199 (67), 186 (2), 172 (11), 154 (13), 139 (3), 129 (17), 102 (10), 90 (8), 85 (9), 77 (4), 70 (26), 57 (16), 51 (3).

7c ($C_{17}H_{18}N_6S$): R = N-methylpiperazino; 76%; m.p.: 191°C; IR (KBr): ν = 2975m, 2820w, 1620m, 1570s, 1550s, 1500s, 1465m, 1440w, 1300w, 1265s, 1170m, 770s, 740s, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 2.35 (s, 3H, CH_3), 2.55 (t, J = 6 Hz, 4H, CH_2NCH_2), 2.62 (s, 3H, CH_3), 3.9 (t, J = 6 Hz, 4H, CH_2NCH_2), 7.3–7.5 (m, 2H, arom-H), 7.8 (m, 1H, arom-H), 8.4 (m, 1H, arom-H) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz); δ = 25.71 (CH_3), 46.01 (NCH_3), 45.58 ($2CH_2$), 54.81 ($2CH_2$), 97.33 (C-2), 113.22, 118.95, 122.21, 124.39, (C-7, C-8, C-9, C-10), 129.93, 148.35, 152.20, 153.04, 157.35, 165.07 (C-4a, C-11a, C-6a, C-10a, C-5a, C-4) ppm; MS: m/z (%) = 339 [M+1] (17), 323 (1), 294 (2), 288 (4), 270 (7), 268 (100), 255 (29), 239 (7), 212 (2), 199 (9), 172 (2), 154 (3), 134 (2), 83 (12), 70 (15), 57 (1).

7d ($C_{16}H_{16}N_6S$): R = piperazino; 55%; m.p.: 210°C; IR (KBr): ν = 3315m, 2945w, 2820w, 1640m, 1570s, 1545s, 1510s, 1460m, 1250s, 1145m, 765s, 745s, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.8 (s, 1H, NH), 2.55 (s, 3H, CH_3), 3.0 (m, 4H, CH_2NCH_2), 3.8 (m, 4H, (CH_2NCH_2), 7.3 (m, 2H, arom-H), 7.6 (m, 1H, arom-H), 8.3 (m, 1H, arom-H) ppm; MS: m/z = 324 [M +1] (34), 294 (15), 282 (46), 268 (73), 256 (100), 241 (14), 239 (19), 199 (26), 162 (19), 154 (11), 134 (11), 129 (13), 109 (15), 91 (12), 83 (17), 69 (27), 57 (16).

4-Azido-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazole (**8**; $C_{12}H_7N_7S$)

Equal amounts of chloro compound **3** (1.0 g, 3.6 mmol) and sodium azide were refluxed in ethanol (15 ml) for 6 h. The resulting precipitate was collected by filtration and crystallized from dioxane to give **8** in 65% yield.

M.p.: 224°C; R = N_3; IR (KBr): ν = 2150s, 1630m, 1615m, 1565s, 1500m, 1460m, 1405s, 1250s, 1190s, 765s, 745s cm^{-1}; ^1H NMR (*TFA*, 90 MHz): δ = 2.95 (s, 3H, CH_3), 7.85 (m, 3H, arom-H), 8.6 (m, 1H, arom-H) ppm; MS: m/z (%) = 281 [M^+] (67), 253 (69), 226 (12), 212 (8), 195 (10), 186 (20), 174 (2), 160 (100), 149 (2), 143 (2), 134 (11), 116 (6), 102 (48), 90 (21), 76 (10), 70 (32), 63 (10), 50 (8).

(2-Methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazol-4-yl)thioacetic acid (**9**; $C_{14}H_{10}N_4O_2S_2$)

A mixture of chloro compound **3** (1.0 g, 3.6 mmol) and mercaptoacetic acid (2.0 ml) was fused without solvent for about 2.0 h. The reaction mixture was cooled, diluted with water, and the resulting precipitate was collected by filtration. The white precipitate was crystallized from ethanol to give white crystals of **9** in 58% yield.

M.p.: 262°C (decomp); R = SCH_2COOH; IR (KBr): ν = 3440w, 2950w, 2900w, 2850w, 1690w, 1615m, 1610m, 1570s, 1490m, 1440s, 1240s, 1030s, 765s, 750s cm^{-1}; ^1H NMR (*TFA*, 90 MHz): δ = 3.1 (s, 3H, CH_3), 4.5 (s, 2H, SCH_2), 7.8 (m, 3H, arom-H), 8.6 (m, 1H, arom-H) ppm; MS: m/z (%) = 330 [M^+] (21), 285 (34), 256 (100), 199 (10), 149 (23), 145 (18), 134 (17), 128 (17), 122 (29), 105 (45), 99 (19), 77 (34), 70 (35), 69 (32), 55 (17).

4-Alkyl/aralkylthio-2-methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazoles (**10a–c**)

Thiol derivative **4** (0.55 g, 2.0 mmol) was dissolved in an aqueous solution of KOH (10%), and alkyl/aralkyl halides in ethanol (5.0 ml) were added dropwise with stirring at room temperature over a period of one hour. The resulting precipitate was collected by filtration, dried, and crystallized from methanol or ethanol to give the corresponding 4-alkyl/aralkylthio-2-methylpyrimidino[4′,5′:4,5]-thiazolo[3,2-*a*]benzimidazoles **10a–c**.

10a ($C_{13}H_{10}N_4S_2$): R = CH_3; 76%; m.p.: 195°C; IR (KBr): ν = 1610m, 1540s, 1525s, 1485s, 1465s, 1245s, 1050m, 760s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.65 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 7.3 (m, 2H, arom-H), 7.6 (m, 1H, arom-H), 8.2 (m, 1H, arom-H) ppm; MS: m/z (%) = 286

[M^+] (100), 285 (53), 253 (8), 241 (17), 228 (17), 212 (3), 199 (26), 187 (3), 172 (5), 154 (6), 134 (6), 129 (11), 102 (8), 90 (7), 73 (3), 70 (23), 51 (1).

10b ($C_{14}H_{12}N_4S_2$): $R = C_2H_5$; 82%; m.p.: 162°C; IR (KBr): ν = 1605m, 1550s, 1525s, 1490s, 1465s, 1240s, 1040m, 760s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.4 (t, J = 7 Hz, 3H, CH_3), 2.7 (s, 3H, CH_3), 3.4 (q, J = 7 Hz, 2H, CH_2), 7.3 (m, 2H, arom-H), 7.65 (m, 1H, arom-H), 8.2 (m, 1H, arom-H); MS: m/z = 300 [M^+] (100), 285 (45), 272 (59), 267 (87), 241 (11), 228 (5), 213 (3), 199 (30), 186 (7), 172 (5), 160 (7), 149 (18), 136 (18), 134 (13), 129 (11), 113 (51), 102 (15), 90 (13), 77 (4), 70 (43), 57 (8).

10c ($C_{19}H_{14}N_4S_2$): $R = CH_2Ph$; 50%; m.p.: 180°C; IR (KBr): ν = 3064m, 3024m, 1616m, 1532s, 1500s, 1464s, 1400s, 1312s, 1244s, 1040s, 760s, 736s cm^{-1}; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 25.89 (CH_3), 33.86 (SCH_2), 105.99 (C-2), 113.00, 119.44, 122.86, 124.84, 127.66, 128.68, 129.20 (arom-C), 129.92, 136.82, 148.49, 150.05, 153.36, 161.90, 165.24 (C-4a, C-11a, C-6a, C-10a, C-5a, C-4) ppm; MS: m/z (%) = 363 [M +1] (23), 362 (M^+] (100), 347 (2), 328 (38), 303 (2), 285 (13), 271 (4), 240 (4), 219 (2), 213 (2), 204 (7), 199 (7), 186 (2), 159 (5), 149 (2), 134 (3), 129 (8), 119 (2), 102 (6), 91 (53), 77 (3), 65 (9), 57 (8), 51 (2).

(2-Methylpyrimidino[4',5':4,5]thiazolo[3,2-a]benzimidazol-4-yl)thioketones (**11a–c**)

A mixture of thiol derivative **4** (0.55 g, 2.0 mmol) and *p*-substituted phenacyl bromide or bromoacetone was refluxed in ethanol (20 ml) for 5–7 hours. The precipitate resulting after cooling was collected by filtration and crystallized from ethanol or dioxane to give **11a–c**.

11a ($C_{15}H_{12}N_4OS_2$): $R = CH_2COCH_3$; 46%; m.p.: 161°C; IR (KBr): ν = 2965m, 1725s, 1615s, 1540s, 1500s, 1470s, 1360s, 1240s, 1040s, 760s, 745s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3 (s, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.0 (s, 2H, SCH_2CO), 7.2 (m, 2H, arom-H), 7.6 (m, 1H, arom-H), 8.1 (m, 1H, arom-H) ppm; MS: m/z (%) = 328 [M^+] (7), 327 [M^{-1}] (32), 312 (1), 285 (35), 284 (100), 271 (3), 254 (2), 239 (5), 212 (2), 199 (19), 186 (2), 160 (2), 154 (7), 149 (1), 134 (4), 129 (4), 102 (7), 90 (6), 77 (1), 70 (35), 63 (3), 50 (2).

11b ($C_{20}H_{13}N_4ClOS_2$): $R = p$-$CH_2COC_6H_4Cl$; 62%; m.p.: 212°C; IR (KBr): ν = 2975w, 2900w, 1690s, 1600s, 1540s, 1500s, 1465s, 1240s, 1090s, 765s, 750s, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.6 (s, 3H, CH_3), 4.85 (s, 2H, SCH_2CO), 7.3–8.1 (m, 7H, arom-H), 8.5 (m, 1H, arom-H) ppm; MS: m/z (%) = 426 [M + 1] (21), 425 [M^+] (26), 424 (52), 287 (23), 285 (100), 219 (34), 141 (29), 139 (97), 112 (23), 111 (36), 91 (26), 88 (38), 70 (25), 58 (26).

11c ($C_{20}H_{13}N_4BrOS_2$): $R = p$-$CH_2COC_6H_4Br$; 35%; m.p.: 217°C; IR (KBr): ν = 2980w, 2900w, 2840w, 1690s, 1585s, 1530s, 1500s, 1470m, 1240s, 1200s, 1080s, 770s, 750s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3 (s, 3H, CH_3), 4.8 (s, 2H, SCH_2CO), 7.4–8.0 (m, 7H, arom-H), 8.4 (m, 1H, arom-H) ppm; MS: m/z (%) = 287 [M-182] (8), 285 [M-184] (19), 210 (21), 197 (12), 181 (11), 167 (12), 154 (27), 149 (17), 141 (14), 139 (13), 134 (10), 129 (13), 125 (22), 118 (11), 111 (29), 105 (19), 91 (24), 85 (50), 81 (44), 77 (17), 71 (66), 69 (68), 63 (11), 57 (100), 51 (14).

(2-Methylpyrimidino[4',5':4,5]thiazolo[3,2-a]benzimidazol-4-yl)thioacetanilides (**12a–c**)

Thiol derivative **4** (0.55 g, 2.0 mmol) was dissolved in an aqueous solution of KOH (10%), and chloroanilide derivatives (2.0 mmol) in ethanol (5.0 ml) were added dropwise with stirring at room temperature over a period of 3 h. The resulting precipitate was collected by filtration, dried, and crystallized from dioxane or ethanol.

12a ($C_{21}H_{17}N_5OS_2$): $R = p$-$CH_2CONHC_6H_4Me$; 38%; m.p.: 245°C; IR (KBr): ν = 3192w, 3056w, 3028w, 1660s, 1608s, 1528s, 1496s, 1468m, 1400s, 1240s, 1036s, 760s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3 (s, 3H, CH_3), 4.4 (s, 2H, SCH_2CO), 7.25 (m, 4H, arom-H), 7.7 (m, 3H, arom-H), 8.55 (m, 1H, arom-H), 9.1 (s, 1H, NHCO) ppm; MS: m/z (%) = 419 [M^+] (16), 313 (24), 312 (100), 294 (18), 286 (71), 272 (20), 262 (34), 251 (15), 240 (11), 234 (11), 223 (32), 219 (22),

199 (15), 178 (21), 165 (13), 149 (9), 135 (55), 119 (8), 107 (29), 102 (9), 91 (15), 83 (35), 77 (16), 55 (12), 47 (8).

12b ($C_{21}H_{17}N_5O_2S_2$): R = p-$CH_2CONHC_6H_4OMe$; 68%; m.p.: 241°C; IR (KBr): ν = 3132w, 3064w, 2996w, 2952w, 2832w, 1664s, 1612s, 1532s, 1508s, 1468m, 1400s, 1244s, 1036s, 760s, 740s, cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 4.35 (s, 2H, SCH_2CO), 6.8–7.9 (m, 7H, arom-H), 8.6 (m, 1H, arom-H), 9.1 (s, 1H, NHCO) ppm; MS: *m/z* (%) = 434 [M −1] (3), 403 (1), 361 (4), 346 (4), 325 (1), 312 (49), 285 (38), 272 (10), 254 (4), 240 (10), 212 (6), 199 (10), 186 (3), 165 (12), 154 (12), 149 (16), 139 (5), 129 (9), 123 (76), 115 (10), 108 (60), 102 (12), 91 (25), 81 (53), 76 (29), 69 (66), 63 (16), 57 (100), 55 (85), 51 (21), 47 (1).

12c ($C_{20}H_{14}N_5BrOS_2$): R = p-$CH_2CONHC_6H_4Br$; 42%; m.p.: 259°C; IR (KBr): ν = 3184w, 3056w, 2980m, 2924m, 1672s, 1588s, 1528s, 1496s, 1468s, 1400s, 1240s, 1036s, 760s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 2.3 (s, 3H, CH_3), 4.4 (s, 2H, SCH_2CO), 7.2–7.9 (m, 7H, arom-H), 8.6 (m, 1H, arom-H), 9.2 (s, 1H, NHCO) ppm; MS: *m/z* (%) = 485 [M +1] (3), 484 [M^+] (1), 449 (1), 411 (4), 390 (1), 361 (2), 346 (2), 328 (2), 312 (100), 296 (1), 285 (76), 272 (27), 254 (8), 241 (15), 228 (10), 212 (9), 199 (20), 186 (6), 171 (31), 154 (20), 149 (14), 139 (4), 129 (16), 102 (24), 91 (29), 77 (18), 70 (83), 63 (29), 57 (53), 51 (23), 47 (2).

(2-Methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazol-4-yl)thioethylacetate (**13**)
and (2-Methylpyrimidino[4′,5′:4,5]thiazolo[3,2-a]benzimidazol-4-yl)thioethylmalonic ester (**14**)

A mixture of thiol derivative **4** (0.55 g, 2.0 mmol), ethyl chloroacetate or diethylbromomalonic ester in dry acetone (20 ml), and anhydrous K_2CO_3 (0.5 g) was refluxed on a water bath for 3 h. The reaction mixture was concentrated till dryness and washed several times with water. The resulting precipitate was collected by filtration and dried well. The crude products were crystallized from ethanol to give the corresponding thioesters **13** and **14** as colourless crystals.

13 ($C_{16}H_{14}N_4O_2S_2$): R = $CH_2COOC_2H_5$; 75%; m.p.: 166°C; IR (KBr): ν = 2984m, 2936m, 1744s, 1616s, 1536s, 1496s, 1468s, 1404s, 1244s, 1040s, 760s cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz): δ = 1.3 (t, J = 7 Hz, 3H, CH_3), 2.7 (s, 3H, CH_3), 4.1 (s, 2H, SCH_2CO), 4.25 (q, J = 7 Hz, 2H, OCH_2), 7.35 (m, 2H, arom-H), 7.7 (m, 1H, arom-H), 8.15 (m, 1H, arom-H); MS: *m/z* (%) = 358 [M^+] (61), 342 (2), 313 (6), 285 (100), 272 (5), 256 (2), 239 (6), 212 (2), 199 (5), 186 (2), 154 (3), 149 (1), 134 (4), 129 (2), 102 (2), 91 (4), 70 (5), 57 (1).

14 ($C_{19}H_{18}N_4O_4S_2$): R = $CH(COOC_2H_5)_2$; 66%; m.p.: 158°C; IR (KBr): ν = 3064w, 2984m, 2936m, 2872w, 1748s, 1616s, 1560s, 1504s, 1468s, 1404s, 1240s, 760s, 740s cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.35 (t, J = 7 Hz, 6H, $2CH_3$), 2.8 (s, 3H, CH_3), 4.35 (q, J = 7 Hz, 4H, $2CH_2$), 5.8 (s, 1H, SCH), 7.45 (m, 2H, arom-H), 7.8 (m, 1H, arom-H), 8.32 (m, 1H, arom-H) ppm; MS: *m/z* (%) = 430 [M^+] (25), 399 (1), 384 (6), 357 (100), 338 (17), 311 (11), 285 (38), 283 (67), 272 (26), 258 (4), 239 (13), 212 (8), 199 (10), 186 (4), 154 (16), 149 (4), 134 (4), 129 (5), 115 (4), 102 (12), 90 (6), 70 (32), 63 (2), 51 (2).

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