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ORIGINAL PAPER

Synthesis of novel 4-(2-amino-5-thiazolyl)-pyrimidine-2-amines as potential protein kinase inhibitors

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Abstract A short and efficient sequence for the synthesis of a series of 4-(2-amino-5-thiazolyl)-pyrimidine-2-amines was developed. 1-Phenyl-2-(6-pyrimidinyl)-ethanones, obtained via Weinreb's methodology, were used in a Hantzsch thiazole cyclization reaction, followed by introduction of the aniline moieties via nucleophilic substitution.

Keywords Fungicides · Heterocycles · Nucleophilic aromatic substitutions · Cyclizations · *Weinreb* amide

Introduction

The lead structure for the development of the phenylaminopyrimidine-type (PAP) protein kinase inhibitors (PKI) was 3-{4-[2-(3-chlorophenylamino)-pyrimidin-4-yl]-pyridin-2-yl-amino}-propanol (CGP 60474) [1]. It led later to the introduction of Imatinib (Gleevec™) as the first PKI in the therapy of leukaemia by Novartis [2–5] (Fig. 1). Additionally, CGP 60474 showed also good biological activity as a fungicide [6, 7].

Continuing work within our research group on this topic led to the synthesis of a series of analogs by modifying the pyridyl-pyrimidine motif. In preceding studies we were particularly interested in the variation of the number and the positions of the ring nitrogens within the lead structure [8–10] (Fig. 2).

Further variations were envisaged by retaining the guanidine structural element of the CGP 60474 system, considered as an essential feature for the biological activity [7–10]. Aiming to improve the fungicidal activity, we report now on the synthesis of the title compounds bearing a thiazole ring in place of the pyridine ring in the PAP-type PKIs [11].

Scheme 1 shows a retrosynthetic analysis of the target system. A crucial step was the preparation of the thiazole motif. The required α-bromoketone precursors for the Hantzsch cyclization should be available via lateral lithiation of **2**, subsequent acylation with a suitable electrophile to give ketones **3**, followed by direct bromination in α-position. Some recent publications also use this strategy for the synthesis of imidazolyl-pyrimidine (p38 kinase inhibitor) [12, 13] and pyrazolopyridinyl-pyrimidine (TNF-α inhibitor) [14] derivatives (Scheme 2).

Results and discussions

Although the pyrimidine derivative **2** could be selectively deprotonated with *LDA* at the methyl group in 4-position, the reaction with benzoyl chloride did not afford the desired ketone. The high reactivity of the acid chloride even at −80 °C gave a mixture of various inseparable products. We therefore switched to less reactive electrophiles, namely *Weinreb* amides [15]. Benzoyl chloride and 4-methoxybenzoyl chloride were reacted with *N*-methoxy-*N*-methylamine to give the desired *Weinreb* amides **1a** [15] and **1b**. Lithiated 4-methyl-2-methylthiopyrimidine (**2**)

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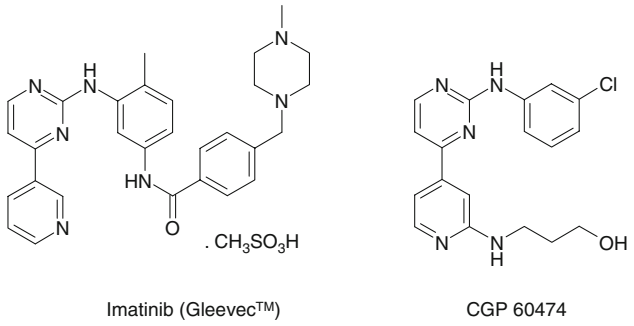


Fig. 1 Lead structures

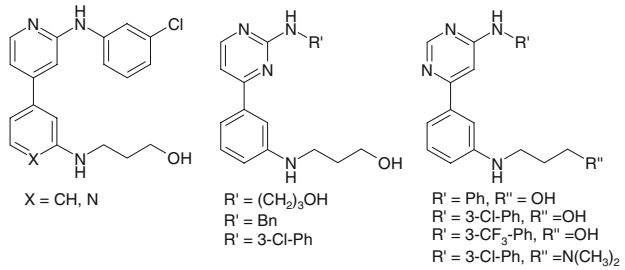


Fig. 2 Modifications from the Stanetty laboratory

afforded ketones **3a** and **3b** (Scheme 3) in very good yields (85 and 94%) and purity upon reaction with amides **1a** and **1b**. It is noteworthy that in solution both ketones are in equilibrium with their enol form in ratios (keto:enol) 1:1.8 for **3a** and 1.7:1 for **3b**.

Bromination of **3a** and **3b** was initially carried out with bromine in chloroform, but the desired compounds could not be obtained. Alternatively, bromination in acetic acid of technical purity (~98%) gave the desired products **4a** and **4b** in good yields. Trace amounts of water were found to be essential for this reaction, as no conversion was observed when the reaction was carried out under comparable conditions in glacial acetic acid. It has to be mentioned that **4a** and **4b** have a limited stability of only a few days when kept at room temperature.

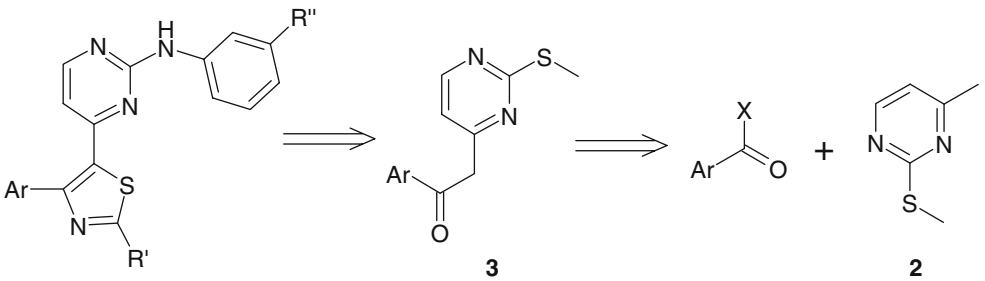
Cyclization reactions of **4a** and **4b** with *N*-substituted thioureas afforded compounds **5a–e** (Table 1, entries A1–A5). Hantzsch reactions with **4a**, *N*-methylthiourea and *N*,*N*-dimethylthiourea were performed in chloroform and triethylamine as base to give **5a** (98%) and **5b** (61%) in good yields (Table 1, Entries A1, A2). In contrast, only *N*,*N*-dimethylthiourea reacted smoothly with **4b** in chloroform and NEt_3 as base to give **5e** in 85% yield (Table 1, entry A5). Reaction with thiourea gave decomposition; changing the solvent to *DMSO* or dioxane also proved unsuccessful. Only in water at reflux temperature and NaOH as base was some conversion observed, and 8% of **5c** was obtained (Table 1, entry A3). 4-Methoxybenzoic acid was isolated as by-product, which is probably formed upon cleavage of **4b**. Further optimization attempts on that reaction failed. In order to obtain product **5c**, we alternatively tried the cyclization with *N*-acetylthiourea, which should give **5c** after deprotection. However, also in this case all cyclization efforts failed.

On the other hand, cyclization of **4b** with *N*-methylthiourea gave the desired product **5d** in 46% overall yield. The structure of **5d** was confirmed by X-ray analysis (Fig. 3).

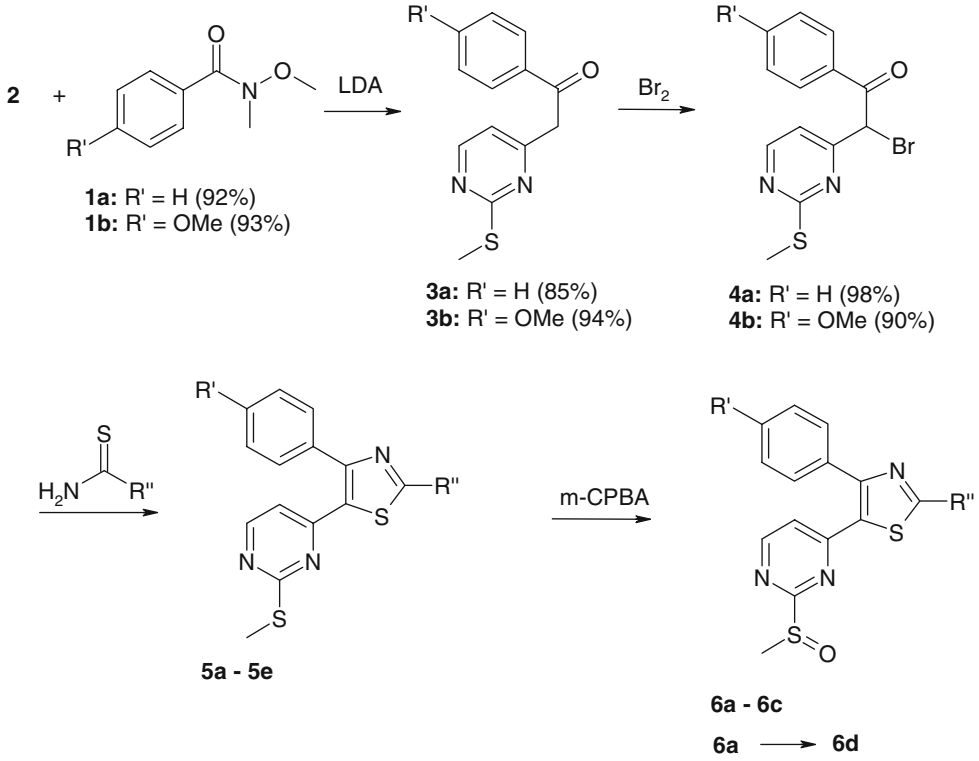
To perform the nucleophilic substitution in 2-position of the pyrimidine ring, the *S*-methyl group had to be oxidized with *m-CPBA*, and the corresponding sulfoxides **6a–c** were obtained in good yields (Table 1, entries B1–B3).

Subsequently, various aniline derivatives were applied in the nucleophilic exchange step. Conversion of **6a** gave no desired products, in all experiments, only decomposed material was observed. Since it was believed that the free NH-proton caused the failure in the nucleophilic exchange reaction, the NHMe group in compound **6a** was protected with an acetyl group to give **6d** in excellent yield (Table 1, entry B4). Still, the exchange reaction with **6d** gave similar disappointing results as for **6a**. The nucleophilic substitution of **6b** and **6c** with aniline, 3-methoxyaniline, and 3-aminoacetophenone afforded the desired products **7a–f**,

Scheme 1



Scheme 2



Scheme 3

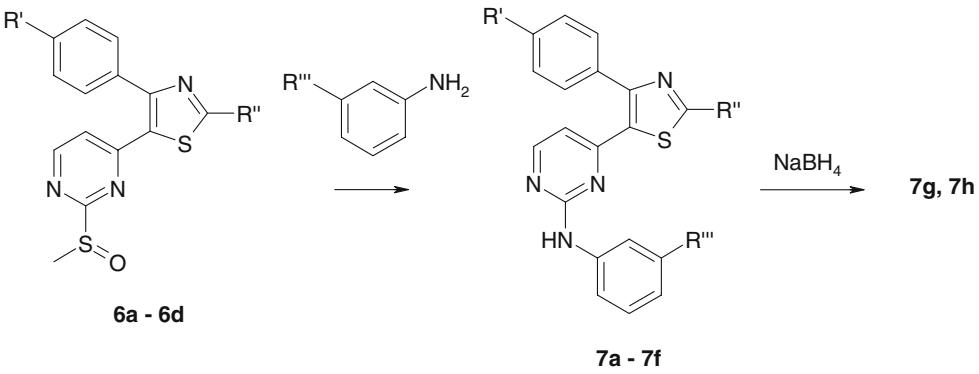


Table 1 Summary of cyclization and oxidation experiments

Entry	Substrate	Product	React. type	Yield (%)	R′	R″
A1	**4a**	**5a**	Cyclization[a]	98	H	NHMe
A2	**4a**	**5b**	Cyclization[a]	61	H	NMe_2
A3	**4b**	**5c**	Cyclization[b]	8	OMe	NH_2
A4	**4b**	**5d**	Cyclization[a]	46	OMe	NHMe
A5	**4b**	**5e**	Cyclization[a]	85	OMe	NMe_2
B1	**5a**	**6a**	Oxidation[c]	99	H	NHMe
B2	**5a**	**6b**	Oxidation[c]	71	H	NMe_2
B3	**5b**	**6c**	Oxidation[c]	85	OMe	NMe_2
B4	**6a**	**6d**	Acylation[d]	96	H	N(Me)Ac

[a] NEt_3, $CHCl_3$, reflux, (**5b**, **5e**: *N*,*N*-dimethylthiourea; **5a**, **5d**: *N*-methylthiourea)

[b] NaOH, H_2O, reflux, thiourea

[c] m-CPBA, $CHCl_3$, rt

[d] NEt_3, acetic anhydride, dioxane, reflux

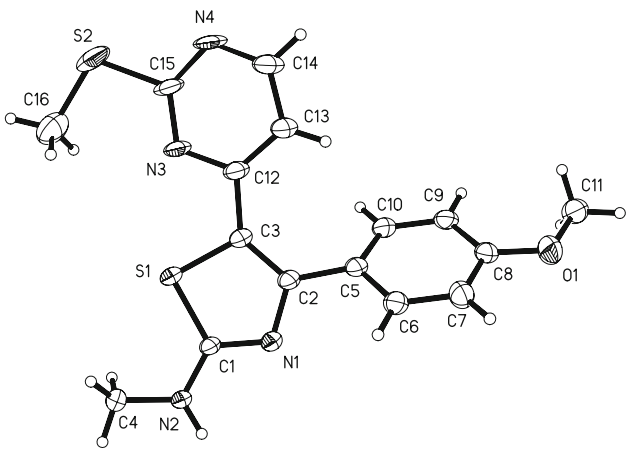


Fig. 3 Crystal structure of **5d**

Table 2 Nucleophilic exchange and reduction reactions to target products

Entry	Starting material	Product	React. type	Yield (%)	R′	R″	R‴
C1	**6b**	**7a**	Nuc. ex[a]	51	H	NMe_2	H
C2	**6b**	**7b**	Nuc. ex[b]	37	H	NMe_2	OMe
C3	**6b**	**7c**	Nuc. ex[c]	18	H	NMe_2	Ac
C4	**6c**	**7d**	Nuc. ex[a]	39	OMe	NMe_2	H
C5	**6c**	**7e**	Nuc. ex[b]	47	OMe	NMe_2	OMe
C6	**6c**	**7f**	Nuc. ex[c]	41	OMe	NMe_2	Ac
C7	**7c**	**7g**	Reduction[d]	99	H	NMe_2	CH(OH)Me
C8	**7f**	**7h**	Reduction[d]	99	OMe	NMe_2	CH(OH)Me

[a] Aniline, BF_3, reflux

[b] 3-Methoxyaniline, BF_3, reflux

[c] 3-Aminoacetophenone, BF_3, dioxane, reflux

[d] $NaBH_4$, EtOH

but the reactions again did not proceed without problems. The crude materials contained considerable amounts of impurities, which made purification by recrystallization and column chromatography mandatory. The cumbersome purification procedure explains the mediocre yields (Table 2, entry C1–C6).

Finally, the carbonyl groups of **7c** and **7f** were reduced with $NaBH_4$ to give the corresponding alcohols **7g** and **7h** in excellent yields (Table 2, entry C7, C8).

Conclusion

The described synthesis shows a straightforward approach to various thiazolyl-pyrimidines as new structural variants of PAP-related PKI. By applying different combinations of substituted *Weinreb* amides and aniline derivatives, this method can easily be extended to the formation of a larger series of such thiazole derivatives. In addition, this method can also be utilized for the synthesis of other heteroaryls.

Experimental

Melting points were determined using a Kofler-type Leica Galen III micro hot-stage microscope and are uncorrected. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm). NMR spectra were recorded from $CDCl_3$ or d_6-*DMSO* solutions on a Bruker AC 200 (200 MHz) spectrometer, and chemical shifts are reported in ppm using TMS as internal standard.

*N,4-Dimethoxy-N-methyl-benzamide (**1b**)*

1b was prepared according to reference [16] in 93% yield, but pyridine was used as base instead of NEt_3. Its identity was proven according to ^1H and ^{13}C NMR spectra.

*2-[2-(Methylthio-4-pyrimidinyl)]-1-phenylethanone (**3a**)*

LDA was prepared following standard procedure under argon atmosphere in 60 cm^3 *THF* with 5.19 g diisopropylamine (51.43 mmol), 21.89 cm^3 2.35 M *n*-butyllithium in *n*-hexane (51.43 mmol). This solution was cooled to −80 °C, and 6.00 g **2** (42.86 mmol) in 20 cm^3 *THF* was added drop wise. The mixture was warmed to −5 °C and stirred for 45 min. Then it was cooled again to −80 °C, and 7.78 g **1a** (47.15 mmol) dissolved in 20 cm^3 *THF* was added slowly. The mixture was warmed to room temperature and then heated overnight at reflux. The mixture was concentrated, hydrolyzed with 2*n* HCl, and extracted with chloroform. The organic layer was washed with water and brine and finally dried over Na_2SO_4. The crude product was purified by Kugelrohr-distillation. Starting material was obtained in a first fraction at 0.01 mbar and 100 °C. Then 8.86 g (85%) of **3a** at 0.01 mbar and 185 °C was isolated. ^1H-NMR (200 MHz, $CDCl_3$): *keto:* $\delta = 2.49$ (s, SCH_3), 4.35 (s, 2H, H2), 6.94 (d, $J = 5.1$ Hz, 1H, H5′), 7.34–7.58 (m, 4H, H2″, 3″, 5″, 6″), 7.76–7.85 (m, 2H, H4″), 8.41 (d, $J = 5.1$ Hz, 1H, H6′); *enol:* 2.57 (s, SCH_3), 5.95 (s, 1H, H2), 6.59 (d, $J = 5.5$ Hz, 1H, H5′), 7.34–7.58 (m, 4H, H2‴, 3″, 5″, 6″), 7.76–7.85 (m, 2H, H4″), 8.26 (d, $J = 5.5$ Hz, 1H, H6′), 14.41–14.62 (bs, OH); ^{13}C-NMR (50 MHz, $CDCl_3$): *keto:* $\delta = 47.3$ (t, C2), 116.5 (d, C5′), 195.0 (s, C1); *enol:* 93.3 (d, C2), 125.7 (d, C5′); *keto and enol:* 13.8 (q, $2SCH_3$), 128.2, 128.3, 128.4, 128.5 (4d, C2″, C3″, C5″, C6″), 130.3, 133.4 (2d, C4″), 134.6, 136.0 (2s, C1″), 155.9, 156.7 (2d, C6′), 163.7, 164.2 (2s, C4′), 167.5, 169.4, 172.4 (3s, C2′, enolic C1).

1-(4-Methoxyphenyl)-2-[2-(methylthio-4-pyrimidinyl)]-ethanone (**3b**, $C_{14}H_{14}N_2O_2S$)

Compound **3b** was prepared following the procedure for **3a** from 2.77 g diisopropylamine (27.68 mmol), 12.2 cm^3 2.27 M *n*-butyllithium in *n*-hexane (27.68 mmol), 4.50 g **2** (23.07 mmol), 3.23 g **1b** (23.07 mmol), 80 cm^3 of dry *THF* under argon-atmosphere. The reaction mixture was stirred for 80 h at reflux. After extraction, the crude product was triturated with diisopropyl ether. This afforded 6.20 g (98%) of **3b** as a brown resin. ^1H-NMR (200 MHz, $CDCl_3$): *keto:* $\delta = 2.51$ (s, SCH_3), 3.84 (s, $ArOCH_3$), 4.30 (s, 2H, H2), 7.99 (d, 2H, $J = 8.8$ Hz, H2″, H6″), 8.41 (d, 1H, $J = 4.9$ Hz, H6′), 14.56–14.63 (bs, 1H, OH); *enol:* 2.58 (s, SCH_3), 3.83 (s, $ArOCH_3$), 5.87 (s, 1H, H2), 6.57 (d, 1H, $J = 5.4$ Hz), 7.77 (d, 2H, $J = 8.8$ Hz, H2″, H6″), 8.23

(d, 1H, $J = 5.4$ Hz, H6′); *keto and enol:* 6.85–6.99 (keto: 3H, phenyl and pyrimidinyl-H; enol: 2H, phenyl and pyrimidinyl-H); ^{13}C-NMR (50 MHz, $CDCl_3$): *keto:* $\delta = 47.3$ (t, C2), 193.5 (s, C1); *enol:* 91.9 (d, C2); *keto and enol forms:* 13.8, 13.9 (2q, SCH_3), 55.2, 55.4 (2q, OCH_3), 112.3, 113.7 (4d, C3″, C5″), 116.4 (2d, C5′), 127.1, 129.1 (2s, C1″), 127.5, 130.9 (4d, C2″, C6″), 155.7, 156.8 (2d, C6′), 161.5, 163.8, 164.1, 164.4 (4s, C4′, C4″), 167.8, 169.2, 172.4 (3s, C2′, enolic C1).

2-Bromo-2-[2-(methylthio-4-pyrimidinyl)]-1-phenylethanone (**4a**, $C_{13}H_{11}BrN_2OS$)

A solution of 9.70 g **3a** (35.4 mmol) in 200 cm^3 acetic acid (98% purity) was cooled to a maximum of 20 °C, and 5.66 g bromine (35.4 mmol) in 50 cm^3 acetic acid was added. After addition, the mixture was stirred overnight at room temperature. The reaction mixture was concentrated almost to dryness, and $NaHCO_3$ solution was added. The mixture was adjusted to basic pH using Na_2CO_3 and extracted with chloroform. The organic layer was washed with water and brine and dried over Na_2SO_4 to afford 8.51 g (83%) of **4a** as brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.35$ (s, SCH_3), 6.16 (s, 1H, H2), 7.26 (d, $J = 5.1$ Hz, 1H, H5′), 7.46 (m, 4H, H2″, H3″, H5″, H6″), 7.91 (d, $J = 7.2$ Hz, 1H, H4′), 8.41 (d, $J = 5.1$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 13.8$ (q, SCH_3), 48.6 (d, C2), 116.2 (d, C5′), 128.6 (d, C3″, C5″), 129.0 (d, C2″, C6″), 133.5 (s, C1″), 133.9 (d, C4″), 157.8 (d, C6′), 163.9 (s, C4′), 172.4 (s, C2′), 189.7 (s, C1).

2-Bromo-1-(4-methoxyphenyl)-2-[2-(methylthio-4-pyrimidinyl)]-ethanone (**4b**, $C_{14}H_{13}BrN_2O_2S$)

The reaction proceeded as described for **4a** with 5.50 g **3b** (20.07 mmol), 3.21 g bromine (20.07 mmol) in 500 cm^3 acetic acid (98% purity) and afforded 7.02 g (99%) of **4b** as a brown oil. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.44$ (s, SCH_3), 3.79 (s, OCH_3), 6.20 (s, 1H, H2), 6.88 (d, $J = 9.0$ Hz, 2H, H3″, 5″), 7.34 (d, $J = 5.1$ Hz, 1H, H5′), 7.96 (d, $J = 9.0$ Hz, 2H, H2″, 6″), 8.50 (d, $J = 5.1$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 13.8$ (q, SCH_3), 48.6 (d, C2), 55.3 (q, OCH_3), 113.8 (2d, C3″, C5″), 116.1 (d, C5′), 126.2 (s, C1″), 131.4 (2d, C2″, 6″), 157.6 (d, C6′), 164.0, 164.1 (2s, C4′, C4″), 172.0 (s, C2′), 188.1 (s, C1).

N-Methyl-5-[2-(methylthio)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**5a**, $C_{15}H_{14}N_4S_2$)

A solution of 2.90 g **4a** (8.97 mmol), 0.97 g *N*-methylthiourea (10.77 mmol), and 1.09 g triethylamine (10.77 mmol) in 50 cm^3 chloroform was stirred at reflux overnight. After cooling to room temperature, the mixture was washed with 2*n* HCl, water and brine and dried over Na_2SO_4. The crude oily product was stirred in diisopropyl ether and gave after filtration 2.54 g (90%) of **5a** as a brown powder. M.p.: 185–189 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.53$ (s, SCH_3), 2.83 (s, NCH_3), 6.49 (d, $J = 5.5$ Hz, 1H, H5′), 7.35–7.55 (m, 5H H2″, H3″, H4″, H5″, H6″), 8.09 (d, $J = 5.5$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 13.9$ (q, SCH_3), 32.3 (q, NCH_3), 110.4 (d, C5′), 119.2 (s, C5), 128.8 (d, C3″, C5″), 129.1 (d, C2″, C6″), 129.9 (d, C4″), 132.8 (s, C1″), 149.9 (s, C4), 156.0 (d, C6′), 157.4 (s, C4′), 171.6, 172.1 (2s, C2, C2′).

N,N-Dimethyl-5-[2-(methylthio)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**5b**, $C_{16}H_{16}N_4S_2$)

To obtain **5b** 1.25 g **4a** (3.87 mmol), 0.52 g *N,N*-dimethylthiourea (5.03 mmol) and 0.30 g triethylamine (5.03 mmol) were dissolved in 30 cm^3 of chloroform. Following the procedure for **5a**, 0.78 g (61%) of **5b** was obtained as brown powder. M.p.: 134–137 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.56$ (s, SCH_3), 3.21 (s, $N(CH_3)_2$), 6.51 (d, $J = 5.5$ Hz, 1H, H5′), 7.42–7.57 (m, 5H, H2″, H3″, H4″, H5″, H6″), 8.02 (d, $J = 5.5$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 14.0$ (q, SCH_3), 40.0 (q, $N(CH_3)_2$), 110.7 (d, C5′), 120.6 (s, C5), 128.7 (d, C3″, C5″), 128.9 (d, C2″, C6″), 129.0 (d, C4″), 136.0 (s, C1″), 155.5 (s, C2), 155.5 (d, C6′), 158.9 (s, C4′), 170.9, 171.7 (2s, C2, C2′).

4-(4-Methoxyphenyl)-5-[2-(methylthio)-4-pyrimidinyl]-thiazol-2-amine (**5c**, $C_{15}H_{14}N_4OS_2$)

To a suspension of 12 mg thiourea (0.16 mmol) in 5 cm^3 water, 50 mg **4b** (0.14 mmol) was added. The mixture was stirred at reflux for 3 h. After cooling to room temperature, 9 mg sodium hydroxide (0.23 mmol) was added, and the solution was stirred for an additional 1 h. The precipitate was filtrated and dissolved in chloroform. This organic layer was washed with 2*n* hydrochloric acid and water. After drying over Na_2SO_4, 4 mg (8%) of **5c** was isolated. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.55$ (s, SCH_3), 3.89 (s, OCH_3), 6.72 (d, $J = 5.4$ Hz, 1H, H5′), 7.01 (d, $J = 8.6$ Hz, 2H, H3″, H5″), 7.50 (d, $J = 8.6$ Hz, 2H, H2″, H6″), 8.20 (d, $J = 5.4$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 14.1$ (q, SCH_3), 55.5 (q, OCH_3), 111.0 (d, C5′), 114.8 (d, C3″, C5″), 130.5 (d, C2″, 6″), 156.6 (d, C6′), 157.2 (s, C4′), 161.3 (s, C4″), 172.7 (s, C2′).

N-Methyl-5-[2-(methylthio)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**5d**, $C_{16}H_{16}N_4OS_2$)

Procedure 1 The reaction proceeded as for **5c** with 14 mg *N*-methylthiourea (0.16 mmol), 50 mg **4b** (0.14 mmol), and 9 mg sodium hydroxide (0.23 mmol) in 5 cm^3 of water, and 8 mg (16%) of **5d** was isolated.

Procedure 2 A solution of 370 mg **4b** (1.05 mmol), 113 mg *N*-methylthiourea (1.26 mmol), and 127 mg triethylamine (1.26 mmol) in 15 cm^3 chloroform was treated

as described for **4a**. After column chromatography (silica gel; ethyl acetate:petroleum ether = 1:2), a first fraction of 51 mg (14%) of pure **5d** was obtained. A second impure fraction of 130 mg was dissolved in hot ethanol and left to crystallize. An additional 115 mg of **5d** was isolated. The overall yield was 166 mg (46%) of a yellow solid. M.p.: 178–182 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.52$ (s, SCH_3), 2.58 (s, NCH_3), 3.85 (s, OCH_3), 6.50 (d, $J = 5.5$ Hz, 1H, H5′), 6.96 (d, $J = 8.5$ Hz, 2H, H3″, H5″), 7.42 (d, $J = 8.5$ Hz, 2H, H2″, H6″), 8.02 (d, $J = 5.5$ Hz, 1H, H6′), 8.50 (s, 1H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 14.0$ (q, SCH_3), 31.9 (q, NCH_3), 55.3 (q, OCH_3), 110.4 (d, C5′), 114.2 (d, C3″, C5″), 119.3 (s, C5), 127.9 (s, C1″), 130.2 (d, C2″, C6″), 154.4 (s, C4), 155.6 (d, C6), 158.8 (s, C4′), 160.3 (s, C4″), 171.8, 172.4 (2s, C2, C2′); X-ray structure determination of **5d**. Data were collected at room temperature on a Bruker SMART APEX CCD area detector system with Mo Kα radiation ($\lambda = 0.71073$ Å) using a narrow frame method. After data integration the structure was solved with direct methods and refined on F^2 using the program SHELXTL. Crystal data: $C_{16}H_{16}N_4OS_2$, $M_r = 344.45$, triclinic, space group P-1 (no. 2), $a = 4.773(2)$ Å, $b = 13.192(12)$ Å, $c = 14.125(6)$ Å, $\alpha = 111.16(2)°$, $\beta = 95.92(1)°$, $\gamma = 92.42(1)°$, $V = 821.9(9)$ Å^3, $Z = 2$, $D_x = 1.392$ g/cm^3, $\mu = 0.333$ mm^{-1}, $T = 297$ K. One thousand nine hundred eighty-five reflections with $\theta < 25.0°$ were measured and used to refine 211 parameters at $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o| = 0.088$, $wR2 = [\Sigma(w(F_o^2 - F_c^2)^2)/\Sigma(w(F_o^2)^2)]^{1/2} = 0.237$ for 1,185 observed data [$I > 2\sigma(I)$]. CCDC 698196 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

4-(4-Methoxyphenyl)-N,N-dimethyl-5-[2-(methylthio)-4-pyrimidinyl]-thiazol-2-amine (**5e**, $C_{17}H_{18}N_4OS_2$)

A solution of 1.50 g **4b** (4.25 mmol), 0.53 g *N,N*-dimethylthiourea (5.10 mmol), and 0.30 g triethylamine (5.03 mmol) in 30 cm^3 of chloroform was treated as described for **4a**. Finally, 1.34 g (88%) of **5e** was isolated as light brown powder. M.p.: 160–163 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.57$ (s, SCH_3), 3.20 (s, $N(CH_3)_2$), 3.87 (s, OCH_3), 6.59 (d, $J = 5.4$ Hz, 1H, H5′), 6.96 (d, $J = 8.7$ Hz, 2H, H3″, H5″), 7.49 (d, $J = 8.7$ Hz, 2H, H2″, H6″), 8.06 (d, $J = 5.4$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 14.0$ (q, SCH_3), 40.0 (q, $N(CH_3)_2$), 55.3 (q, OCH_3), 110.6 (d, C5′), 114.1 (d, C3″, C5″), 120.0 (s, C5), 128.1 (s, C1″), 130.4 (d, C2″, C6″), 155.3 (d, C6′), 155.4 (s, C4), 159.1, 160.2 (s, C4′, C4″), 170.8, 171.6 (2s, C2, C2′).

N-Methyl-5-[2-(methylsulfinyl)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**6a**, $C_{15}H_{14}N_4OS_2$)

A solution of 1.20 g **5a** (3.82 mmol) in 25 cm^3 of chloroform was cooled with an ice bath, and 1.32 g *m-CPBA* (60% purity) (4.60 mmol) was added in five portions within 1 h. The mixture was warmed to room temperature and stirred an additional 1.5 h. This solution was washed with sat. $NaHCO_3$ solution and brine and then dried over Na_2SO_4; 1.23 g (98%) of **6a** was isolated. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.65$ (s, $SOCH_3$), 2.94 (s, NCH_3), 6.78 (d, $J = 5.6$ Hz, 1H, H5′), 7.39–7.52 (m, 5H, H2″, H3″, H4″, H5″, H6″), 8.34 (d, $J = 5.6$ Hz, 1H, H6′), ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 31.8$ (q, NCH_3), 39.9 (q, $SOCH_3$), 115.0 (d, C5′), 118.4 (s, C5), 128.6 (d, C3″, C5″), 129.1 (d, C2″, C6″), 129.6 (d, C4″), 135.3 (s, C1″), 156.4 (s, C4), 156.6 (d, C6′), 159.8 (s, C4′), 173.1 (2s, C2, C2′).

N,N-Dimethyl-5-[2-(methylsulfinyl)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**6b**, $C_{16}H_{16}N_4OS_2$)

To a solution of 0.52 g **5b** (1.58 mmol) in 20 cm^3 of chloroform, 0.42 g *m-CPBA* (60% purity) (1.58 mmol) was added following the procedure for **6a**. After warming to room temperature, the solution was stirred for an additional 5 h. Then 0.15 g *m-CPBA* was added, and the mixture was stirred overnight at room temperature. Workup proceeded as for **6a** and afforded 0.52 g (96%) of **6b**. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.87$ (s, $SOCH_3$), 3.12 (s, $N(CH_3)_2$), 6.74 (d, $J = 5.6$ Hz, 1H, H5′), 7.36–7.48 (m, 5H, H2″, H3″, H4″, H5″, H6″), 8.24 (d, $J = 5.6$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 39.9$ (q, $SOCH_3$), 40.1 (q, $N(CH_3)_2$), 115.2 (d, C5′), 119.3 (s, C5), 128.8 (d, C3″, C5″), 129.0 (d, C2″, C6″), 129.4 (d, C4″), 135.6 (s, C1″), 156.4 (d, C6′), 157.6 (s, C4), 160.1 (s, C4′), 171.4 (s, C2), 172.9 (s, C2′).

4-(4-Methoxyphenyl)-N,N-dimethyl-5-[2-(methylsulfinyl)-4-pyrimidinyl]-thiazol-2-amine (**6c**, $C_{17}H_{18}N_4O_2S_2$)

A solution of 1.20 g **5e** (3.35 mmol) in 20 cm^3 of chloroform was cooled with an ice bath. During 1 h, while being cooled, 1.10 g *m-CPBA* (60% purity) (4.02 mmol) was added in five portions. After stirring at room temperature for 7 h, additional 0.30 g *m-CPBA* was added, and the mixture was stirred at room temperature overnight. Workup proceeded as for **6a** and afforded 1.24 g (99%) of **6c**. ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.95$ (s, $SOCH_3$), 3.21 (s, $N(CH_3)_2$), 3.88 (s, OCH_3), 6.92 (d, $J = 5.7$ Hz, 1H, H5′), 6.98 (d, $J = 8.7$ Hz, 2H, H3″, H5″), 7.48 (d, $J = 8.7$ Hz, 2H, H2″, H6″), 8.35 (d, $J = 5.7$, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 39.9$ (q, $SOCH_3$), 40.0 (q, $N(CH_3)_2$), 55.3 (q, OCH_3), 114.3 (d, C3″, C5″), 115.2 (d, C5′), 118.8 (s, C5), 127.8 (s, C1″), 130.2 (d, C2′, C6′),

156.3 (d, C6′), 157.6 (s, C4), 160.4, 160.5 (2s, C4′, C4″), 171.4 (s, C2), 173.0 (s, C2′).

N-Acetyl-N-methyl-5-[2-(methylsulfinyl)-4-pyrimidinyl]-4-phenyl-thiazol-2-amine (**6d**, $C_{17}H_{16}N_4O_2S_2$)

A solution of 0.44 g **6a** (1.33 mmol), 0.16 g acetic anhydride (1.60 mmol), and ten drops of triethylamine (catalytic) in 10 cm^3 of dry dioxane was stirred overnight at reflux. The mixture was concentrated and chloroform was added. The organic layer was washed with saturated Na_2CO_3 solution, water, and brine and dried over Na_2SO_4. This procedure afforded 0.47 mg (95%) of **6d**. M.p.: 98–100 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.45$ (s, $SOCH_3$), 2.94 (s, $N(CH_3)_2$), 3.75 (s, $COCH_3$), 7.07 (d, $J = 5.4$ Hz, 1H, H5′), 7.39–7.56 (m, 5H, H2″, H3″, H4″, H5″, H6″), 8.52 (d, $J = 5.4$ Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 23.0$ (q, CH_3), 35.1 (q, NCH_3), 39.8 (q, $SOCH_3$), 117.3 (d, C5′), 125.2 (s, C5), 128.8 (d, C3″, C5″), 128.9 (d, C2″, C6″), 129.3 (d, C4″), 135.0 (s, C1″), 152.0 (s, C4), 157.6 (d, C6′), 160.5, 161.0 (2s, C2, C4′), 170.5 (s, CO), 173.5 (s, C2′).

4-(2-Dimethylamino-4-phenyl-5-thiazolyl)-N-phenyl-pyrimidin-2-amine (***7a***, $C_{21}H_{19}N_5S$)

A solution of 140 mg **6b** (0.41 mmol) and three drops of borontrifluoride etherate (catalytic) in 5 cm^3 of aniline was stirred at reflux overnight. A main part of the aniline was separated by Kugelrohr distillation, and the concentrated mixture was dissolved in chloroform. This layer was washed with 2*n* hydrochloric acid, satd. Na_2CO_3 solution, water, and brine. The organic layer was dried over Na_2SO_4. The crude product was dissolved in a small amount of ethyl acetate and precipitated with petroleum ether. This solid was filtered over 500 wt% silica gel with ethyl acetate and afforded 77 mg (50%) of **7a**. M.p.: 211–215 °C; ^{1}H-NMR (200 MHz, *DMSO*-d^6): $\delta = 3.12$ (s, $N(CH_3)_2$), 6.20 (d, $J = 5.4$ Hz, 1H, H5), 6.92–7.74 (m, 10H, ArH), 8.06 (d, $J = 5.4$ Hz, 1H, H6), 9.45 (s, NH); ^{13}C-NMR (50 MHz, *DMSO*-d^6): $\delta = 39.7$ (q, $N(CH_3)_2$), 106.5 (d, C5), 118.8 (d, C2″), 120.4 (d, C4″), 121.3 (s, C5′), 128.4 (d, C3‴, C5‴), 128.7 (d, C2‴, C6‴), 128.9 (d, C4‴), 136.1 (s, C1‴), 140.5 (s, C1″), 154.2 (s, C4′), 157.0 (d, C6), 158.6 (s, C4), 159.5 (s, C2), 169.7 (s, C2′).

4-(2-Dimethylamino-4-phenyl-5-thiazolyl)-N-(3-methoxyphenyl)-pyrimidin-2-amine (**7b**, $C_{22}H_{21}N_5OS$)

A solution of 200 mg **6b** (0.58 mmol) and three drops of borontrifluoride etherate (catalytic) in 5 cm^3 of 3-methoxyaniline was treated as described for **7a**. After precipitation, the product was purified by column chromatography over silica gel. The eluent was petroleum ether and ethyl acetate in a ratio of 4:1. This procedure afforded 86 mg (37%) of **6b**. M.p.: 160–162 °C; ^{1}H-NMR (200 MHz, *DMSO*-d^6): $\delta = 3.11$ (s, $N(CH_3)_2$), 3.78 (s, OCH_3), 6.20 (d, $J = 5.4$ Hz, 1H, H5), 6.48–7.61 (m, 9H, ArH), 7.74 (d, $J = 8.0$ Hz, 2H, H2‴, H6‴), 8.06 (d, $J = 5.4$ Hz, 1H, H6), 9.47 (s, NH); ^{13}C-NMR (50 MHz, *DMSO*-d^6): $\delta = 39.6$ (q, $N(CH_3)_2$), 55.0 (q, OCH_3), 104.2 and 106.4 (2d, C2″, C4″), 107.0 (d, C6″), 111.2 (d, C5), 120.4 (s, C5′), 128.6 (d, C3‴, C5‴), 128.6 (d, C2‴, C6‴), 128.9 (d, C4‴), 129.1 (d, C5″), 136.0 (s, C1‴), 141.8 (s, C1″), 154.2 (s, C4′), 157.0 (d, C6), 158.4 (s, C4), 159.5 (s, C3″), 169.6, 169.7 (2s, C2, C2′).

1-[3-[[4-(2-Dimethylamino-4-phenyl-5-thiazolyl)-2-pyrimidinyl]-amino]-phenyl]-ethanone (**7c**, $C_{23}H_{21}N_5OS$)

To a solution of 520 mg **6b** (1.51 mmol) and 750 mg 3-aminoacetophenone (5.56 mmol) in 10 cm^3 of dry dioxane, five drops of borontrifluoride etherate (catalytic) were added. The mixture was stirred at reflux overnight. The dioxane was removed by distillation and the residue dissolved in chloroform. Further workup proceeded as for **7a**. Final purification with column chromatography was done on silica gel with petroleum ether and ethyl acetate in a 2:1 ratio and 2.5 vol% triethylamine. This procedure afforded 115 mg (18%) of **7c** as yellow powder. M.p.: 212–214 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 2.70$ (s, 3H, H2), 3.25 (s, $N(CH_3)_2$), 6.39 (d, $J = 5.4$ Hz, 1H, H5″), 7.32–7.77 (m, 9H, ArH), 8.02 (d, $J = 5.4$ Hz, 1H, H6″), 8.47 (s, NH); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 27.0$ (q, C2), 40.1 (q, $N(CH_3)_2$), 108.0 (d, C5″), 118.6 and 123.4 (2d, C2′, C4′), 121.0 (s, C5‴), 122.0 (d, C6′), 128.7, 129.0, 129.0 and 129.2 (4d, C5′, C2‴′, C3‴′, C4‴′, C5‴′, C6‴′), 136.2 (s, C1‴′), 137.9 (s, C3′), 140.2 (s, C1′), 155.3 (s, C4″), 156.4 (d, C6″), 159.1, 159.8 (2s, C2‴, C4‴), 170.7 (s, C2″), 198.1 (s, C1).

4-[4-(4-Methoxyphenyl-2-dimethylamino-5-thiazolyl)]-N-phenyl-pyrimidin-2-amine (**7d**, $C_{22}H_{21}N_5OS$)

A solution of 135 mg **6c** (0.36 mmol) in 5 cm^3 of aniline was treated as described for **7a**. Final purification was performed by column chromatography over silica gel and petroleum ether:ethyl acetate = 3:1 as eluent and afforded 56 mg (39%) of **7d** as a brown solid. M.p.: 228–232 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): $\delta = 3.13$ (s, $N(CH_3)_2$), 3.81 (s, OCH_3), 6.32 (d, $J = 5.3$ Hz, 1H, H5), 6.93–7.76 (m, 9H, ArH), 8.09 (d, $J = 5.3$ Hz, 1H, H6), 9.45 (bs, NH); ^{13}C-NMR (50 MHz, $CDCl_3$): $\delta = 39.6$ (q, $N(CH_3)_2$), 55.2 (q, OCH_3), 106.4 (d, C5), 113.9 (d, C3‴, C5‴), 118.7 and 121.1 (2d, C2″, C3″, C5″, C6″), 119.7 (s, C5′), 128.1 (s, C1‴), 128.4 (d, C4″), 130.3 (d, C2‴, C6‴), 140.5 (s, C1″), 154.0 (s, C4′), 156.9 (d, C6), 158.7, 159.5, 159.6 (3s, C2, C4, C4‴), 169.5 (s, C2′).

N-(3-Methoxyphenyl)-4-[4-(4-methoxyphenyl-2-dimethylamino-5-thiazolyl)]-pyrimidin-2-amine (**7e**, $C_{23}H_{23}N_5O_2S$)

A solution of 384 mg **6c** (1.03 mmol) in 5 cm^3 of 3-methoxyaniline was treated as described for **7b**. Final

purification was performed with column chromatography over silica gel and petroleum ether:ethyl acetate = 2:1 as eluent and afforded 210 mg (47%) of **7e** as a green solid. M.p.: 170–172 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.21 (s, $N(CH_3)_2$), 3.89 and 3.91 (2s, $2OCH_3$), 6.44 (d, J = 5.5 Hz, 1H, H5), 6.62–7.59 (m, 8H, ArH), 8.03 (d, J = 5.5 Hz, 1H, H6); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 40.0 (q, $N(CH_3)_2$), 55.3 and 55.4 (2q, $2OCH_3$), 104.5 and 107.7 (2d, C2″, C4″), 108.1 (d, C6″), 111.3 (d, C5), 114.1 (d, C3‴, C5‴), 120.6 (s, C5′), 128.5 (s, C1‴), 129.4 (d, C5″), 130.5 (d, C2‴, C6‴), 141.1 (s, C1″), 154.7 (s, C4′), 156.5 (d, C6), 159.4, 159.8 (2s, C2, C4), 160.1, 160.2 (2s, C3″, C4‴), 170.4 (s, C2′).

1-[3-[[4-(2-Dimethylamino-4-(4-methoxyphenyl)-5-thiazolyl)-2-pyrimidinyl]-amino]-phenyl]-ethanone (**7f**, $C_{24}H_{23}N_5O_2S$)

A solution of 500 mg **6c** (1.34 mmol) and 450 mg 3-aminoacetophenone (3.33 mmol) in 10 cm^3 of dioxane was treated according to the procedure for **7c**. Final purification was performed with column chromatography over silica gel and petroleum ether:ethyl acetate = 1:1 with 2.5 vol% triethylamine and afforded 244 mg (41%) of **7f** as a yellow solid. M.p.: 213–217 °C; ^{1}H-NMR (200 MHz, *DMSO*-d^6): δ = 2.70 (s, 3H, H2), 3.24 (s, $N(CH_3)_2$), 3.89 (s, OCH_3), 6.48 (d, J = 4.9 Hz, 1H, H5″), 6.99–7.77 (m, 8H, ArH), 8.04 (d, J = 4.9 Hz, 1H, H6″), 8.46 (bs, NH); ^{13}C-NMR (50 MHz, *DMSO*-d^6): δ = 27.0 (q, C2), 40.1 (q, $N(CH_3)_2$), 55.4 (q, OCH_3), 107.8 (d, C5″), 114.1 (2d, C3‴, C5‴), 118.7, 122.1, 123.5 (3d, C2′, C4′, C6′), 120.4 (s, C5‴), 128.4 (s, C1‴), 129.0 (d, C5′), 130.5 (d, C2‴, C6‴), 137.9 (s, C3′), 140.1 (s, C1′), 155.5 (s, C4″), 155.7 (d, C6″), 158.8, 160.2, 160.3 (3s, C2‴, C4‴, C4‴), 170.7 (s, C2″), 198.1 (s, C1).

1-[3-[[4-(2-Dimethylamino-4-phenyl-5-thiazolyl)-2-pyrimidinyl]-amino]-phenyl]-ethanol (**7g**, $C_{23}H_{23}N_5OS$)

To a suspension of 45 mg **7c** (0.11 mmol) in 5 cm^3 of dry ethanol, 20 mg of $NaBH_4$ (0.54 mmol) was added. The mixture was stirred overnight at reflux. After removing the ethanol by distillation, the residue was dissolved in ethyl acetate and washed with water. The organic layer was dried over Na_2SO_4 and the solvent evaporated, yielding 44 mg (99%) of **7g** as a yellow powder. M.p.: 157–159 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.59 (d, J = 6.5 Hz, 3H, H2), 3.23 (s, $N(CH_3)_2$), 4.95 (q, J = 6.5 Hz, 1H, H1), 6.34 (d, J = 5.5 Hz, 1H, H5″), 7.05–7.62 (m, 9H, ArH), 7.96–8.01 (m, 2H, H6‴ and NH); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 25.2 (q, C2), 40.1 (q, $N(CH_3)_2$), 70.6 (d, C1), 107.5 (d, C5″), 116.0, 118.1 and 119.1 (3d, C2′, C4′, C6′), 121.4 (s, C5″), 128.7, 128.9, 128.9 and 129.2 (4d, C5′, C2⁗/C6⁗, C3⁗/C5⁗, C4⁗), 136.2 (s, C1⁗), 140.0 (s, C3′), 146.9 (s, C1′), 154.9 (s, C4″), 156.6 (d, C6″), 159.4, 159.5 (2s, C2‴, C4‴), 170.6 (s, C2″).

1-[3-[[4-(2-Dimethylamino-4-(4-methoxyphenyl)-5-thiazolyl)-2-pyrimidinyl]-amino]-phenyl]-ethanol (**7h**, $C_{24}H_{25}N_5O_2S$)

A suspension of 100 mg **7c** (0.11 mmol) and 40 mg $NaBH_4$ (1.08 mmol) in 15 cm^3 of ethanol was treated as described for **7g**. After workup 99 mg (99%) of **7h** was isolated as a yellow solid. M.p.: 89–91 °C; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.58 (d, J = 6.5 Hz, 3H, H2), 2.19–2.29 (bs, 1H, OH), 3.22 (s, $N(CH_3)_2$), 3.89 (s, OCH_3), 4.95 (dq, J^1 = 12.9 Hz, J^2 = 6.5 Hz, 1H, H1), 6.43 (d, J = 5.6 Hz, 1H, H5′), 6.94–7.53 (m, 8H, ArH), 7.95 (bs, NH), 8.00 (d, J = 5.6 Hz, 1H, H6′); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 25.2 (q, C2), 40.0 (q, $N(CH_3)_2$), 55.3 (q, OCH_3), 70.6 (d, C1), 107.3 (d, C5″), 114.1 (d, C3⁗, C5⁗), 116.1, 118.2, 119.3 (3d, C2′, C4′, C6′), 120.7 (s, C5″), 128.4 (s, C1⁗), 128.9 (d, C5′), 130.5 (d, C2⁗, C6⁗), 139.8 (s, C3′), 146.9 (s, C1′), 155.3 (s, C4″), 155.7 (d, C6″), 158.9, 160.0, 160.2 (3s, C2‴, C4‴, C4⁗), 170.6 (s, C2″).

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