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A very concise synthesis of a potent *N*-(1,3-thiazol-2-yl)pyridin-2-amine KDR kinase inhibitor

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Abstract—A very concise synthesis of a potent KDR kinase inhibitor **1** is described. The synthesis features an exceedingly efficient one-pot preparation of the aminothiazole **6** followed by Pd–Xantphos catalyzed cross-coupling with chloropyridine aldehyde **11**. Reductive amination of the resulting aldehyde **10** with the piperazine fragment **9** afforded the final product.

1. Introduction

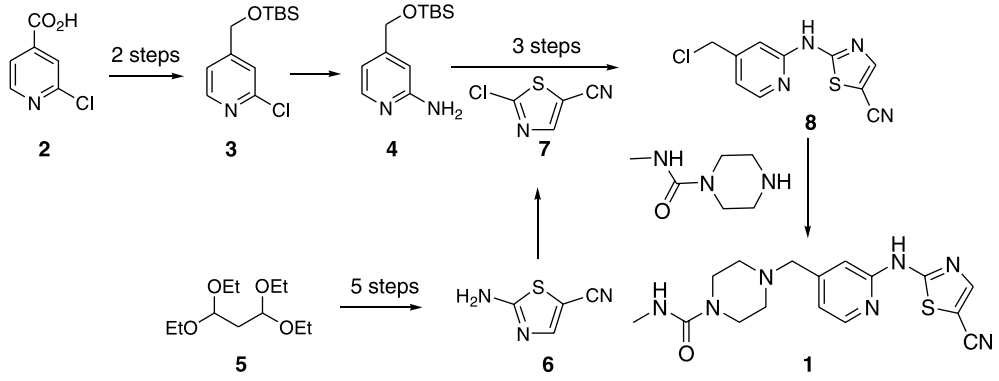
Angiogenesis, the growth of new blood vessels, is promoted by vascular endothelial growth factor (VEGF). The kinase insert domain-containing receptor (KDR) is a tyrosine kinase-linked receptor for VEGF. Inhibition of KDR has been shown to inhibit tumor angiogenesis and the growth of tumors in animal models.[1]

Recent efforts at Merck led to the discovery of a potent and orally active KDR kinase inhibitor **1**.[2] The reported synthesis of the target molecule required a total of 14 steps from commercially available starting materials (Scheme 1).

One feature of the synthesis we wished to avoid was the functional group and protecting group manipulation at the 4-position of the pyridine. Additionally, a reverse polarity coupling of a chloropyridine **3** with aminothiazole **6** would remove an additional two steps. We also sought a shorter synthesis of the thiazole fragment **6**.[3] We envisioned that the most efficient synthetic scheme would involve a direct coupling of the aminothiazole **6** with 2-chloropyridine aldehyde **11** (Scheme 2). The resulting aldehyde **10** could then be directly connected to the piperazine fragment **9** by reductive amination.

2. Results and discussion

Although Pd-catalyzed arylation of amines has attracted a large amount of attention in the past few years,[4] there are few examples of Pd-catalyzed N-arylation of heteroarylamines. Among these examples, no functional groups on the aryl halides or the arylamines were present.[5,6] Additionally,



Scheme 1. Medicinal chemistry synthesis.

Keywords: KDR; Pd-catalysis; Xantphos; Aminothiazole; Chloropyridine; Piperazine.
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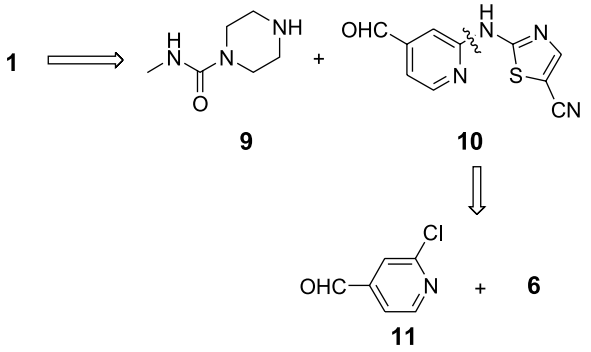


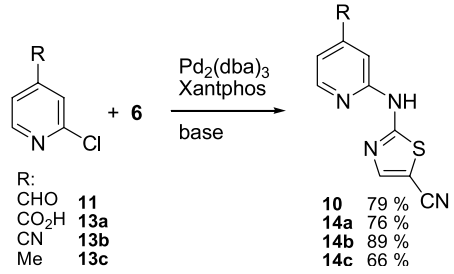
Scheme 2. Retrosynthetic analysis.

N-arylation of an aminothiazole had not been reported at all in the literature despite the important biological activities of 2-arylaminothiazoles.[7] Attempted coupling of aminothiazole **6** with chloropyridine aldehyde **11** under palladium catalysis failed to give any desired coupling product **10** using literature procedures. The reaction conditions were indeed too harsh to tolerate the aldehyde functional group. We were also unsuccessful in attempts using analogous copper catalyzed coupling. Thus, development of a new Pd-catalyzed N-arylation that can tolerate the sensitive aldehyde functional group was required to implement our synthetic strategy.

The main cause for the failure was likely due to decomposition of the aldehyde in the presence of a strong base such as KO^{t}Bu. Thus, screening experiments were carried out with milder bases such as K_3PO_4, Na_2CO_3, K_2CO_3, Cs_2CO_3 etc. We found that many ligands that are generally successful for Pd-catalyzed carbon–nitrogen bond forming reactions with some functional group compatability[4] such as BINAP, DPEphos, DPPF, P(*o*-Tol)$_3$, DPPB, and phosphinobiphenyls[8] gave either no reaction or decomposition due to the presence of the aldehyde group. Only Xantphos[9] gave significant amounts of the desired product **10**. Solvent screening indicated that toluene was the solvent of choice. More polar solvents led to rapid decomposition of **11**. Commercial powdered K_3PO_4 was found to give better results than granular material. Under optimized reaction conditions, the coupling product was obtained in as high as 83% assay yield.

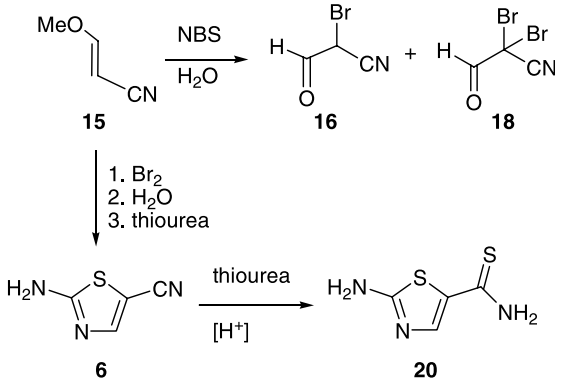
Subsequently, we found that scale up from a sealed Schlenk tube to a septum-capped flask connected to nitrogen line led to incomplete conversion. Rigorous purification of the starting materials and more careful exclusion of air/moisture did not improve the outcome. The only rationale for the low conversion appeared to be the loss of water in an unsealed system. Indeed, addition of 0.5–1.0 equiv of water restored the reaction profile. By maintaining the water content in the reaction vessel, the reaction can be scaled up reproducibly. The role of water in the reaction is unclear. It might retard the formation of imine or make K_3PO_4 a more soluble and more effective base.

2-Chloropyridines with different substituents could also be efficiently coupled with aminothiazole **6** (Scheme 3). Note the carboxylic acid group was also tolerated. The less activated substrate **13c** required a higher catalyst loading. The Pd–Xantphos catalyst system proved to be general for N-arylation of heteroaryl amines, and the results from our laboratories were published recently.[10]



Scheme 3. Pd-catalyzed coupling of 2-chloropyridines.

With the key coupling step established, the search for a more efficient synthesis of the aminothiazole was initiated. We envisioned that bromination of inexpensive 3-methoxyacrylonitrile (**15**) followed by reaction with thiourea and subsequent cyclization should deliver the desired aminothiazole **6** quickly (Scheme 4). The starting material **15** was available as a ~2:1 *E*/*Z* mixture. The presence of *E*/*Z* isomers should be inconsequential, however.



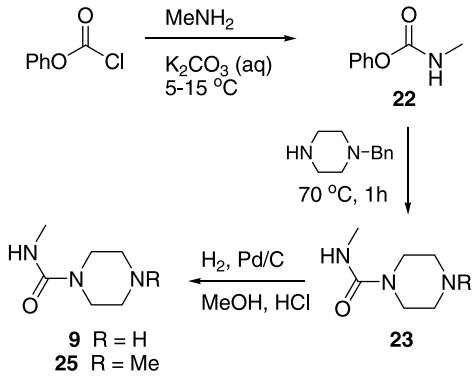
Scheme 4. Preparation of aminothiazole.

Treatment of **15** with NBS in MeOH followed by thiourea and aqueous HCl failed to give any aminothiazole **6**. The surprisingly sluggish hydrolysis of the dimethylacetal intermediate was likely the problem. Thus, the reaction was carried out in aqueous acetonitrile to directly give aldehyde **16**. This approach was, however, complicated by the formation of the dibromo aldehydre **18**. On the other hand, in dry acetonitrile, bromine reacted with **15** almost instantaneously at 0 °C affording the dibromo adduct, which was easily hydrolyzed to **16** in situ by simply adding water. Subsequent reaction with thiourea followed by cyclization at 60 °C afforded aminothiazole **6**. However, the yield was only 30%. The main product was identified to be the thioamide **20**,[11] formed by reaction of the aminothioazole **6** and excess thiourea[12] under strongly acidic conditions. By neutralizing the generated HBr with NaOAc, we were able to improve the yield of **6** to 78% after carbon treatment and recrystallization. Thus, we have developed an efficient, economical and high yielding one-pot synthesis of the aminothiazole **6**.

Although the piperazine fragment **9** can be made from methyl isocyanate[13] and mono-protected piperazine, the toxicity of methyl isocyanate makes it undesirable for large scale use. The most common methods for the

preparation of unsymmetrical ureas use alkyl or aryl chloroformates to take advantage of the substantial reactivity differences of the two reactive sites.[14] Phenyl chloroformate is ideal due to its relatively low cost and enhanced reactivity of the carbamate for the urea formation step.

Methylamine was reacted first to obviate issues with its low boiling point as the urea formation step required somewhat elevated temperature. Thus phenyl chloroformate was added to a biphasic mixture of methylamine, K_2CO_3 in acetonitrile and water to give the carbamate intermediate **22** (Scheme 5). Rapid addition of phenyl chloroformate and efficient cooling were required to avoid significant hydrolysis of **22**.

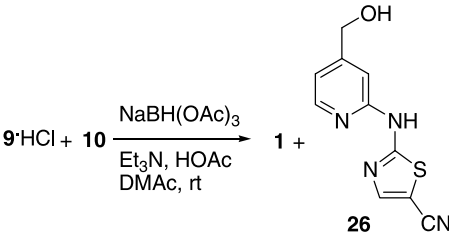


Scheme 5. Piperazine fragment.

The carbamate was not isolated but directly reacted with *N*-benzyl-piperazine. Using unprotected piperazine was not viable due to severe bis-acylation problem. The reaction was carried out at 70 °C furnishing **23** as a crystalline dihydrate in 87% yield. The benzyl protecting group was then removed by a simple hydrogenolysis in MeOH with 5% Pd/C to give the desired product **9**. Interestingly, a small amount of methylation product **25** was observed with higher catalyst loading (20 wt% of 10% Pd/C). Since compound **9** is a viscous oil, it was isolated as its crystalline HCl salt in 83% overall yield based on *N*-benzyl-piperazine.

With both partners **9** and **10** in hand, the final coupling step via a reductive amination was investigated (Eq. 1).[15]

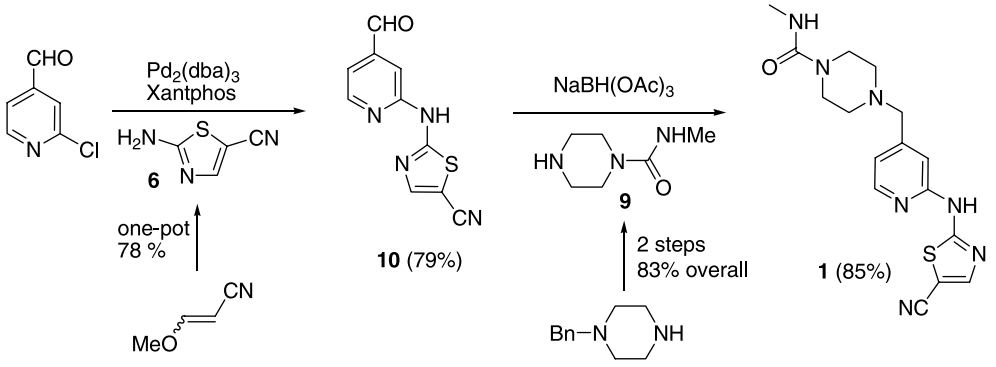
We found that the reaction was very sluggish in THF with $NaBH(OAc)_3$ and 5 equiv of HOAc, giving only 25% conversion after stirring at rt overnight. Furthermore, the undesired alcohol **26** was the main product. It was found that polar solvents such as DMF, DMAc, NMP or DMSO gave much better results. DMAc was selected for better impurity rejection and more controlled crystallization.



(1)

Approximately 4–5 equiv of acetic acid seemed optimal for the reaction. The selectivity for reductive amination versus aldehyde reduction increased from 60:40 to 93:7 as HOAc was increased from 0.5 to 5 equiv. Further increase afforded negligible improvement. Strong acids such as MsOH gave mixed results. With 0.5 equiv of MsOH, the selectivity was 84:15, but with 1.0 equiv of MsOH, the selectivity decreased to 73:27 and the reaction was also slower. Using the HCl salt of piperizine **9** directly instead of the free base for the reductive amination resulted in significantly lower selectivity (**1**:**26**=83:17). Fortunately, this problem was easily remedied by adding 1.1 equiv of Et_3N. The optimal temperature for the reaction was 15–25 °C. Lowering the temperature to 0–5 °C decreased the reaction rate without noticeable selectivity enhancement. Addition of $NaBH(OAc)_3$ in portions provided better results than addition in one portion.[16] With the optimized reaction conditions, the final product **1** was isolated in 85% yield.

Thus, we have developed a very concise and convergent synthesis of a potent thiazolyl pyridine KDR inhibitor **1** (Scheme 6). The longest sequence is only three steps and the total number of steps is only five. The overall yield was 52% from 3-methoxyacrylonitrile or 71% from *N*-benzylpiperazine. Key discoveries include a new Pd catalyzed N-arylation of aminothioazole that can tolerate an aldehyde functional group and an exceedingly efficient one-pot synthesis of the aminothiazole **6**.



Scheme 6. Overall synthesis of **1**.

3. Experimental

3.1. General

All commercial chemicals were used as is unless otherwise noted. ^{1}H and ^{13}C NMR spectra were measured at 400 and 100 MHz, respectively.

3.1.1. 2-Amino-thiazole-5-carbonitrile (6). Bromine (2.88 kg, 18 mol) was added to a solution of 3-methoxy-acrylonitrile (1.50 kg, 18.0 mol, ~2:1 *E*/*Z* mixture) in acetonitrile (3.0 L) at 0–5 °C. The mixture was stirred for 20 min then cold water (~5 , 12 L) was added. After vigorous stirring for 1 h, $NaOAc \cdot 3H_2O$, (2.21 kg, 16.2 mol) was added and the stirring continued for 15 min. Thiourea (1.51 kg, 19.8 mol) was added and the mixture was stirred at 5–10 °C for 2 h. More $NaOAc \cdot 3H_2O$ (1.47 kg, 10.8 mol) was added and the reaction mixture was heated to 60 °C over 1 h and stirred for 3 h. The reaction mixture was cooled to 10 °C and the pH adjusted to 3.8–4.0 with NaOH (10 N, 1.1 L) to crystallize the product. The product was filtered, washed with water and then dried to afford 1.93 kg of the crude aminothiazole as a brown solid in 96.6% purity. It was purified by treatment with Darco KB-B (384 g) in acetone (36 L) at 50 °C. The mixture was filtered at 50 °C and the filtrate was concentrated in vacuo to 6.5 kg. Heptane (9.6 L) was added slowly. The product was filtered, washed with 2:1 heptane/acetone and dried to furnish 1.79 kg of **6** as a pinkish solid, 78% yield corrected for 98.2% purity. Mp 210–230 °C (dec); ^{1}H NMR (DMSO-d_6) δ 8.10 (s, 2H), 7.81 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 173.1, 152.5, 114.2, 89.4; IR (KBr, cm^{-1}) 3346, 3277, 2206, 1636, 1491, 1231, 1060. Anal. Calcd for $C_4H_3N_3S$: C, 38.39; H, 2.42; N, 33.58; S, 25.62. Found: C, 38.28; H, 2.36; N, 33.34; S, 25.27.

3.1.2. 2-Amino-thiazole-5-carbothioic acid amide (20). A mixture of aminothiazole **6** (657 mg, 95%, 5.0 mmol) and thiourea (456 mg, 6.0 mmol) in MeCN (2 mL) and H_2SO_4 (10 N, 2 mL) was stirred at 60 °C for 1.5 h then cooled to rt. It was neutralized with NaOH (10 N) until pH=8–9. The acetonitrile was distilled off. Water (5 mL) was added and the product was filtred and air dried affording 557 mg of **20** dihydrate as a yellow solid (17.5% water). ^{1}H NMR (DMSO-d_6) δ 9.00 (s, 1H), 8.94 (s, 1H), 7.64 (s, overlapping NH_2 and C_4–H, 3H); ^{13}C NMR (DMSO-d_6) δ 187.7, 174.4, 139.8, 129.4.

3.1.3. 5-(4-Formyl-pyridin-2-ylamino)-thiazole-2-carbonitrile (10). A mixture of chloropyridine **11** (1.49 kg, 10.5 mol), 2-aminothiazole **6** (1.27 kg, 10.0 mol), powdered K_3PO_4 (2.34 kg, 11.0 mol), $Pd_2(dba)_3$ (114.5 g, 0.125 mol), Xantphos (159 g, 0.275 mol) and toluene (20 L) was degassed and then heated to 60 °C. After slowly adding degassed water (90 mL, 5.0 mol), the mixture was heated to 90 °C and stirred for 8 h. The reaction mixture was then cooled to rt and the crude product was collected by filtering and washing with toluene. DMAc (24 L) was added to the crude product solid and the insoluble material was filtered off. The filtrate was acidified with concentrated HCl (110 mL) to pH 2.7 and then water (3 L) was added. The mixture was concentrated under vacuum with slow addition of water (3 L) to remove most of the toluene. More water (14 L) was very slowly added to crystallize the product, which was filtered and washed sequentially with 5:4 DMAc/water, water and acetone, and then dried at 40 °C under vacuum to give 1.92 kg of **10** in 79% yield corrected for 94.5% purity. Mp 291–292 °C; ^{1}H NMR (DMSO-d_6) δ 12.51 (br s, 1H), 10.01 (s, 1H), 8.58 (d, J=5.2 Hz, 1H), 8.25 (s, 1H), 7.48 (s, 1H), 7.41 (d, J=5.2 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 193.2, 163.4, 151.8, 150.8, 148.3, 144.2, 115.7, 114.5, 111.5, 95.8; IR (polyethylene, cm^{-1}) 2216, 1708, 1618, 1553, 1438, 1408, 1243, 825. HRMS calcd for $(M+H)^+$ $C_{10}H_7N_4OS$ 231.03351, found 231.03447.

3.1.4. 2-(4′-Carboxy-2′-pyridylamino)-5-cyanothiazole (14a). Under nitrogen, a re-sealable Schlenk tube was charged with $Pd_2(dba)_3$ (13.8 mg, 3% Pd), Xantphos (26.0 mg, 4.5%), aminothiazole **6** (132 mg, 1.05 mmol, 1.05 equiv), 2-chloro-4-pyridine carboxylic acid (159 mg, 1.0 mmol, 1.0 equiv), Na_2CO_3 (256 mg, 2.4 mmol, 2.4 equiv), and dioxane (4 mL). Water (18 mg, 1.0 mmol, 1.0 equiv) was added dropwise while stirring the mixture. The Schlenk tube was quickly sealed and immersed into a 100 °C oil bath. After 16 h, the mixture was cooled, filtered, and washed with toluene and water and 1 N HCl. After drying the crude solid, it was recrystallized from DMAc (acidified with aqueous HCl) and water to give the product as a yellow solid (187 mg, 76%). Mp>300 °C; ^{1}H NMR (DMSO-d_6) δ 13.65 (br s, 1H), 12.39 (br s, 1H), 8.48 (d, J=5.1 Hz, 1H), 7.23 (s, 1H), 7.57 (s, 1H), 7.40 (d, J=5.1 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 166.1, 163.4, 151.5, 150.7, 147.7, 141.0, 116.6, 114.5, 111.7, 95.6; IR (polyethylene, cm^{-1}) 3261, 2223, 1699, 1619, 1551, 1382, 763. Anal. Calcd for $C_{10}H_6N_4O_2S$: C, 48.78; H, 2.46; N, 22.75. Found: C, 48.57; H, 2.22; N, 22.38.

3.1.5. 2-(4′-Cyano-2′-pyridylamino)-5-cyanothiazole (14b). Following similar procedure as **14a** but using K_3PO_4 (1.2 equiv) as base, toluene (4 mL) as solvent, and 0.5 equiv of water (without the HCl wash in the workup) gave compound **14b** as a yellow solid (201 mg, 89%). Mp >300 °C; ^{1}H NMR (DMSO-d_6) δ 12.56 (s, 1H), 8.59 (dd, J=5.2, 0.6 Hz, 1H), 8.29 (s, 1H), 7.44 (dd, J=5.2, 0.6 Hz, 1H), 7.41 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 163.0, 151.2, 150.8, 148.4, 121.6, 118.6, 117.1, 114.6, 114.3, 96.2; IR (polyethylene, cm^{-1}) 2246, 2220, 1621, 1544, 1435, 1395. HRMS calcd for $(M+H)^+$ $C_{10}H_6N_5S$ 228.0338, found 228.0349.

3.1.6. 2-(4′-Methyl-2′-pyridylamino)-5-cyanothiazole (14c). The reaction was carried out following similar procedure as **14a** but using 8 mol% of Pd, 1.4 equiv of **6**, Na_2CO_3 (2.0 equiv) as base, and toluene (8 mL) as solvent. The reaction mixture was cooled, diluted with THF and then filtered. The filtrate was concentrated and the residue was purified by silica gel column chromatography followed by recrystallization in toluene to give compound **14c** as a brown solid (142 mg, 66%). Mp 292–293 °C; ^{1}H NMR (DMSO-d_6) δ 12.09 (br s, 1H), 8.19 (br s, 2H), 6.89 (s, 1H), 6.87 (d, J=4.9 Hz, 1H), 2.28 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 163.7, 150.8, 150.7, 150.0, 146.2, 119.4, 114.8, 111.8, 95.1, 21.2; IR (polyethylene, cm^{-1}) 2215, 1622, 1440, 1147. HRMS calcd for $(M+H)^+$ $C_{10}H_9N_4S$ 217.0542, found 217.0553.

3.1.7. 4-Benzyl-piperazine-1-carboxylic acid methylamide (23). Phenyl chloroformate (2.59 kg) was added to a mixture of aqueous K_2CO_3 (4.56 kg in 6.0 L water), acetonitrile (12 L) and methylamine (40 wt% in water, 1.40 kg) as rapidly as possible while maintaining the exothermic reaction at 0–15 °C. After stirring for 15 min, 1-benzyl-piperazine (2.65 kg) was added and the mixture was heated to 70 °C and stirred for 1 h. The reaction mixture was concentrated under vacuum to remove the MeCN. NaOH (5 N, 7.5 L) was added and the mixture was seeded and then cooled to rt to crystallize the product. It was filtered and washed with cold 0.5 N aqueous NaOH, ice-cold water and dried to give 3.59 kg of the dihydrate of **23**, 87% yield. Mp 99–100 °C; ^{1}H NMR (DMSO-d_6) δ 7.32–7.24 (m, 5H), 6.37 (q, J=4.4 Hz, 1H), 3.45 (s, 2H), 3.25 (t, J=4.9 Hz, 4H), 2.55 (d, J=4.4 Hz, 3H), 2.82 (t, J=4.9 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 158.4, 138.4, 129.3, 128.6, 127.4, 62.5, 52.9, 43.8, 27.5. Anal. Calcd for $C_{13}H_{19}N_3O$: C, 66.92; H, 8.21; N, 18.01. Found: C, 66.93; H, 8.14; N, 18.17.

3.1.8. Piperazine-1-carboxylic acid methylamide hydrochloride (9·HCl). HCl (12 N, 74 mL) was added to MeOH (7 L) and then *N*-benzylpiperizine **23** dihydrate (2.69 kg, 10.0 mol) was added. The mixture was hydrogenated using 5% Pd/C (180 g) under 40 psi of hydrogen pressure at 40 °C for 18 h. The mixture was filtered and concentrated. *i*-PrOH (5 L) was added followed by HCl (12 N aqueous, 0.77 L) until the pH of the solution reached ~3. The mixture was then concentrated under vacuum and flushed with more *i*-PrOH until the water content was <1%. After stirring at 15 °C for 5 h, the crystallized product was filtered, washed with *i*-PrOH and dried to give 1.53 kg of **9**·HCl in 95% yield. Mp 185.5–187.0 °C; ^{1}H NMR (DMSO-d_6) δ 9.51 (br s, 2H), 6.79 (q, J=4.3 Hz, 1H), 3.53 (t, J=5.2 Hz, 4H), 2.98 (t, J=5.2 Hz, 4H), 2.55 (d, J=4.3 Hz, 3H); ^{13}C NMR (DMSO-d_6) δ 157.6, 42.4, 40.4, 27.1. Anal. Calcd for $C_6H_{14}ClN_3O$: C, 40.11; H, 7.85; N, 23.39; Cl, 19.73. Found: C, 39.99; H, 7.73; N, 23.22; Cl, 19.91.

3.1.9. 4-[2-(2-Cyano-thiazol-5-ylamino)-pyridin-4-ylmethyl]-piperazine-1-carboxylic acid methylamide (1). $NaBH(OAc)_3$ (2.54 kg, 12.0 mol) was added in six portions (0.5 h/portion) to a mixture of pyridine aldehyde **10** (2.44 kg, 94.5 wt%, 10.0 mol), piperazine urea **9**·HCl salt (1.99 kg, 11.0 mol), DMAc (15 L), Et_3N (1.53 L, 11.0 mol) and acetic acid (2.29 L, 40.0 mol) with slight cooling (15 °C). After stirring for 1 h, water (7.5 L) was slowly added to complete the crystallization. The product was filtered, washed sequentially with 2:1 DMAc/water, 1:1 acetone/water, and acetone, dried at 100 °C to give 3.07 kg of **1** in 85% yield. Mp 248–249.5 °C; ^{1}H NMR (DMSO-d_6) δ 12.16 (s, 1H), 8.30 (d, J=5.3 Hz, 1H), 8.24 (s, 1H), 7.12 (s, 1H), 7.01 (dd, J=5.3, 0.9 Hz, 1H), 6.40 (q, J=4.4 Hz, 1H), 3.50 (s, 2H), 3.28 (t, J=4.7 Hz, 4H), 2.55 (d, J=4.3 Hz, 3H), 2.33 (t, J=4.7 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 163.1, 157.9, 150.4, 150.2, 145.9, 117.7, 114.2, 110.6, 94.6, 60.6, 52.5, 43.3, 27.1; IR (KBr, cm^{-1}): 2209, 1622, 1552, 1446, 1265, 1147, 1007, 882, 786. Anal. Calcd for $C_{16}H_{19}N_7OS$: C, 53.76; H, 5.36; N, 27.43; S, 8.97. Found: C, 53.63; H, 5.27; N, 27.41; S, 8.79.

Acknowledgements

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