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General and Facial Synthesis of 2-Amino-5-halogenpyrimidine-4-carboxylic Acids and Their Derivatives

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General and Facial Synthesis of 2-Amino-5-halogenpyrimidine-4-carboxylic Acids and Their Derivatives

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Abstract: A facile synthetic approach to 2-amino-5-halogen-pyrimidine-4-carboxylic acids from 5-halogen-2-methylsulfonylpyrimidine-4-carboxylic acid by nucleophilic displacement of the methylsulfonyl group with primary and secondary aliphatic amines has been developed. The titled amino acids underwent decarboxylation, yielding 2-amino-5-halogenpyrimidines. Starting from 2-amino-5-chloropyrimidine-4-carboxylic acid chlorides, 2-[5-chloro-2-(amino)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)-ethyl cyanides were obtained in excellent yields.

Keywords: amino acids, aminopyrimidines, nucleophilic substitution, regioselectivity

INTRODUCTION

In the field of medicinal chemistry, substituted 2-aminopyrimidines are one of the most important structural motifs, existing within many pharmaceutically useful compounds. For example, Trimethoprim and Tetroxoprim are famous bactericides,[1a] and Mizolastine is known as an effective histamine H1-receptor antagonist.[1b,c] Substituted 2-amino-5-halogen-pyrimidine-4-

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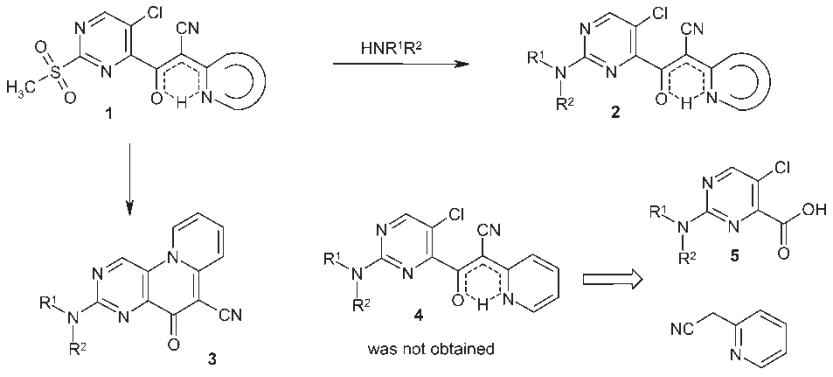


Scheme 1.

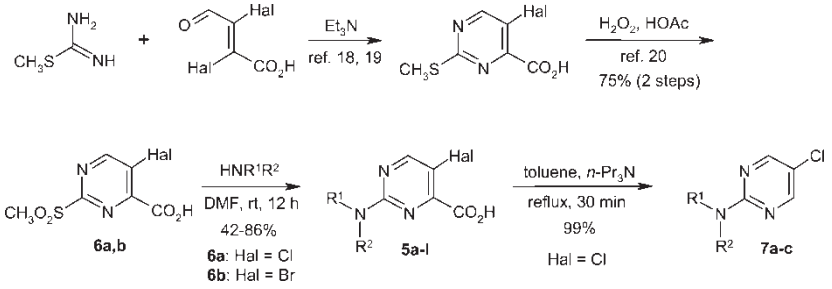
carboxylic acid derivatives have been shown to possess anti-AIDS,[2] bactericidal,[3] antihypertensive, and antithrombozytic activity[4] and are known as effective uridine phosphorylase and DHO DHase inhibitors.[5,6] Furthermore, these compounds have also been used as starting materials in the synthesis of new anti-Alzheimer's pharmaceuticals[7] and other biologically active compounds.[3,8]

Known routes for preparing the titled compounds are limited to primary pyrimidine-ring synthesis,[9] oxidation of the alkyl groups on the C-4(6) position,[10] or functionalization of an NH_2-group in 2-amino-5-halogen-pyrimidine-4-carboxylic acid.[3] Therefore, only a few representatives of this class of amino acids are known. Recently, we have developed a flexible and general approach to cyanides **2** using nucleophilic displacement of the methylsulfonyl group in **1** by amines (Scheme 1).[11–13]

In the case of the pyridine derivative, the reaction afforded condensed pyridopyrimidines **3** as the only isolable products.[12] This fact prompted us to look for alternative approaches to compounds **4**, based on 2-amino-5-halogen-pyrimidine-4-carboxylic acids **5** as starting materials. Because of the lack of a general method for the synthesis of amino acids **5**, herein we describe our results for a facile synthesis and synthetic application of these compounds.

RESULTS AND DISCUSSION

It is known that the methylsulfonyl group in the second position of the pyrimidine ring can be readily substituted by nucleophiles.[14] Moreover, such substitution occurs easily and faster when compared to 2-chloro- and 2-(alkyl)mercaptopyrimidines, and this was successfully applied in the so-called sulfinate catalysis.[15–17] Therefore, our approach was based on functional group manipulations of existing pyrimidine derivatives (Scheme 2). The starting 5-halogen-2-methylsulfonyl-pyrimidine-4-carboxylic acids **6a**,**b**

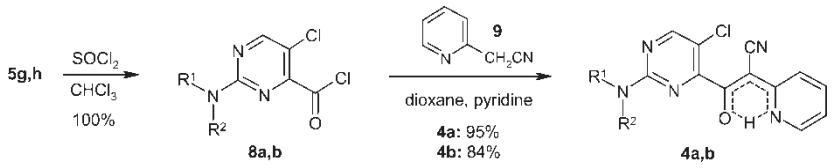


Scheme 2.

were obtained by condensation of *S*-methylisothiourea with mucochloric (or mucobromic) acid,[18,19] followed by oxidation of the methylmercapto group[19,20] to give **6a**,**b** in 75% overall yield. Treatment of **6a**,**b** with aliphatic amines in dimethylformamide at ambient temperature afforded the amino acids **5a**–**l**. Thus, the reaction occurs regioselectively with substitution of the methylsulfonyl group, yielding desired products in synthetically useful yields (Table 1). Gratifyingly, the procedure was scalable, and we were able to conduct this reaction on a 25 mmol scale, generating 4.87 g (80% isolated yield) of **5h**. In spite of their simple structures, all synthesized compounds **5a**–**l** are hitherto unknown representatives of 2-amino-5-halogen-pyrimidine-4-carboxylic acids.[21]

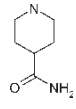
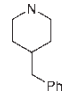
The compounds **5a**–**l** were fully characterized by their analytical and spectroscopic properties. Their ^{1}H NMR spectra revealed signals of an amine moiety along with a one-proton singlet at 8.42–8.48 ppm assigned to the proton at the C-6 position of the pyrimidine ring. The location of an amine moiety at the C-2 position of the ring was uniquely confirmed by two-dimensional NMR experiments, namely heteronuclear multiple bond correlation (HMBC) and heteronuclear single quantum correlation (HSQC). The IR spectra of compounds **5a**–**l** showed absorption bands at 1720–1700 cm^{-1}. This indicated that in the solid state amino acids **5** presumably exist in their acid and not in the betaine form. All substances **5a**–**l** decomposed with release of a gas during melting-point determination. The crystals formed after cooling did not dissolve in $NaHCO_3$ solution. Because pyrimidine-2- and 4-carboxylic acids are known to undergo thermal decarboxylation,[14,19] we assumed that the acids **5** were undergoing a decarboxylation. This decarboxylation was also observed under heating in toluene with a catalytic amount of tripropylamine. This led to the spectroscopically pure aminopyrimidines **7a**–**c** in almost quantitative yields (Scheme 2). Therefore the procedure described represents a new and simple synthetic method of 2-amino-5-halogenpyrimidines, which were reported to possess a variety of biological activities.[22–24]

The acids **5g**,**h** were reacted with thionyl chloride in chloroform and afforded acid chlorides **8a**,**b** quantitatively. When compounds **8a**,**b** were treated with pyridine-2-yl-acetonotrile **9** in the presence of pyridine in dioxane,



Scheme 3.

Table 1. Substituents for compounds **4**, **5**, and **7***a*

Compound	NR^1R^2
5a, **7b**	
5b	
5c	
5d, **7b**	
5e	
5f	
5g, **7c**, **8a**, **4a**	
5h, **I**, **8b**, **4b**	
5i	
5j	
5k	

[a]Hal = Br for **5l**; for other compounds Hal = Cl.

the desired 2-[5-chloro-2-(amino)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)-ethyl cyanides **4a**,**b** were obtained as the only products in excellent yields (Scheme 3).

To test the generality of this approach, other 2-azahetarylacetonitriles (e.g., 1-methyl-benzimidazol-2-yl-acetonitrile and benzothiazol-2-yl-acetonitrile) were studied. In all cases, *C*-acylated derivatives of type **2** (Scheme 1) were obtained. Hence, this method represents an alternative synthetic approach toward the earlier described 2-[5-chloro-2-(amino)-4-pyrimidinyl]-2-oxo-1-(2-hetaryl)-ethyl cyanides.[11,12]

In conclusion, our investigation has successfully provided a general and facile synthesis of substituted 2-amino-5-halogen-pyrimidine-4-carboxylic acids that is amenable to the preparation of a variety of 2-amino-pyrimidine derivatives. This study also established a new strategy for the synthesis of cyanides **2** and represents the only method available for the preparation of substituted 2-[5-chloro-2-(amino)-4-pyrimidinyl]-2-oxo-1-(2-pyridyl)-ethyl cyanides **4**. These reactions are also readily scaled, generating multigram quantities of the 2-amino-pyrimidine derivatives, compounds that can be used as synthetic building blocks and as scaffolds for combinatorial synthesis.

EXPERIMENTAL

Melting points were determined using an Electrothermal melting-point apparatus and are uncorrected. IR spectra were obtained on a Nicolet impact 400 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-300 or Bruker Avance 500 spectrometer. MS were determined on a Varian 212 instrument at 70 eV. Elemental analyses (C, H, N) were conducted using the Perkin-Elmer CHN 240 A or 240 B.

General Procedure for Preparation of Substituted 2-Amino-5-halogen-pyrimidine-4-carboxylic acids 5a–l

To a solution of the corresponding 2-methylsulfonyl-5-halogen-pyrimidine-4-carboxylic acid **6a**,**b** (5 mmol) in dimethylformamide (10 mL), an appropriate amine (15 mmol) was added, and the mixture was stirred at room temperature for 12 h. The solvent was then removed in vacuo (temperature of the water bath did not to exceed 70°C). The residue was dissolved in water (5–10 mL), neutralized with 0.2 N HCl, and left overnight at 8–10°C. The precipitated crystals were collected by filtration and washed with cold water (2 mL) to give usually pure compounds. For further purification (if necessary), the acids were recrystallized from a water–ethanol (4 : 6) mixture.

Data

2-Benzylamino-5-chloropyrimidine-4-carboxylic acid 5a. Yield (75%). Pale yellow crystals, mp 161–162°C (dec.). ^{1}H NMR (500 MHz, DMSO-

d_6): $\delta = 8.42$ (1H, s, pyrim-H), 8.26 (1H, br. s, NH), 7.40–7.20 (5H, m, Ar*H*), 4.62 (2H, d, *J* 6.26 Hz, -*CH*$_2$-NH). (COOH proton was not observed, probably due to exchange with water in DMSO-d_6). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 164.5$, 159.8, 158.0, 140.9, 127.8, 127.7, 126.6, 126.2, 112.0, 43.7. IR ν_{max} (KBr): 3290 (NH), 1710 (COOH) cm^{-1}. Anal. calcd. for $C_{12}H_{10}ClN_3O_2$: C, 54.66;H, 3.82; N, 15.94. Found: C, 54.83; H, 3.65; N, 15.80.

5-Chloro-2-(phenylethylamino)-pyrimidine-4-carboxylic acid 5b. Yield (83%). Pale yellow crystals, mp 171.5–172.5°C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.96$ (1H, br. s, COOH), 8.43 (1H, s, pyrim.-H), 7.83 (1H, br. s, NH), 7.26 (5H, m, Ar*H*), 3.46 (2H, m, CH$_2$*CH*$_2$-NH), 2.83 (2H, t, *J* 7.2 Hz, *CH*$_2$CH$_2$-NH). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 164.9$, 160.1, 158.3, 157.1, 139.4, 128.7, 128.6, 126.0, 112.0, 42.5, 34.5. IR ν_{max} (KBr): 3290 (NH), 1710 (COOH) cm^{-1}. Anal. calcd. for $C_{13}H_{12}ClN_3O_2$: C, 56.23; H, 4.36; N, 15.13. Found: C, 56.02; H, 4.37; N, 14.98.

2-Butylamino-5-chloropyrimidine-4-carboxylic acid 5c. Yield (60%). Pale yellow crystals, mp 110–111.5°C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.79$ (1H, br. s, COOH), 8.44 (1H, s, pyrim.-H), 7.84 (1H, br. s, NH), 3.11 (2H, m, -CH$_2$CH$_2$-NH), 1.48 (2H, m, -*CH*$_2$CH$_2$), 1.27 (2H, m, -*CH*$_2$CH$_3$), 0.87 (3H, t, *J* 7.2 Hz, CH$_3$). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 165.1$, 160.2, 158.4, 156.9, 111.6, 40.5, 30.6, 19.5, 13.6. IR ν_{max} (KBr): 3280 (NH), 1710 (COOH) cm^{-1}. Anal. calcd. for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.30. Found: C, 47.38; H, 5.59; N, 18.28.

5-Chloro-2-diethylaminopyrimidine-4-carboxylic acid 5d. Yield (76%). Pale yellow crystals, mp 116–117°C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): $\delta = 10.05$ (1H, br. s, COOH), 8.44 (1H, s, pyrim.-H), 3.65 (4H, q, *J* 7.3 Hz, *CH*$_2$CH$_3$), 1.17 (6H, t, *J* 7.3 Hz, CH$_2$*CH*$_3$). ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 165.1$, 158.1, 157.4, 156.5, 111.6, 40.5, 19.5. IR ν_{max} (KBr): 1710 (COOH) cm^{-1}. MS (EI): m/z (%): 229 (31) [M$^+$], 214 (100), 200 (14), 183 (33), 168 (26), 154 (16), 140 (40), 128 (12), 56 (13). Anal. calcd. for $C_9H_{12}ClN_3O_2$: C, 47.07; H, 5.27; N, 18.30. Found: C, 47.11; H, 5.27; N, 18.34.

5-Chloro-2-dipropylamino-pyrimidine-4-carboxylic acid 5e. Yield (62%), mp 105–106.5°C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): $\delta = 10.09$ (1H, br. s, COOH), 8.42 (1H, s, pyrim.-H), 3.57 (4H, m, *CH*$_2$-N-*CH*$_2$), 1.65 (4H, m, *CH*$_2$CH$_3$), 0.90 (6H, t, *J* 7.2 Hz, CH$_2$*CH*$_3$). IR ν_{max} (KBr): 1710 (COOH) cm^{-1}. Anal. calcd. for $C_{11}H_{16}ClN_3O_2$: C, 51.27; H, 6.26; N, 16.30. Found: C, 51.41; H, 6.50; N, 16.44.

5-Chloro-2-(pyrrolidin-1-yl)-pyrimidine-4-carboxylic acid 5f. Yield (78%). Pale yellow crystals, mp 160–161°C (dec.). ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 13.12$ (1H, br. s, COOH), 8.47 (1H, s, pyrim.-H), 3.45 (4H, m, *CH*$_2$-N-*CH*$_2$), 1.92 (4H, m, -*CH*$_2$*CH*$_2$-). ^{13}C NMR (75 MHz, DMSO-d_6):

$\delta = 165.1$, 158.1, 157.6, 156.7, 111.5, 46.6, 24.9. IR ν_{max} (KBr): 1710 (COOH) cm^{-1}. Anal. calcd. for $C_9H_{10}ClN_3O_2$: C, 47.48; H, 4.43; N, 18.46. Found: C, 47.67; H, 4.12; N, 18.50.

5-Chloro-2-(piperidin-1-yl)-pyrimidine-4-carboxylic acid 5g. Yield (78%). Pale yellow crystals, mp 127.5–128.5°C (dec.). ^1H NMR (500 MHz, DMSO-d_6): $\delta = 14.10$ (1H, br. s, COOH), 8.48 (1H, s, pyrim.-H), 3.71 (4H, m, CH_2-N-CH_2), 1.63 (4H, m, $2CH_2$), 1.52 (2H, m, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 165.0$, 158.8, 158.4, 156.5, 111.6, 44.5, 25.1, 24.0. IR ν_{max} (KBr): 1710 (COOH) cm^{-1}. Anal. calcd. for $C_{10}H_{12}ClN_3O_2$: C, 49.70; H, 5.00; N, 17.39. Found: C, 49.79; H, 4.90; N, 17.39.

5-Chloro-2-(morpholin-4-yl)-pyrimidine-4-carboxylic acid 5h. Yield (77%). Pale yellow crystals, mp 119.5–120.5°C (dec.). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 13.70$ (1H, br. s, COOH), 8.48 (1H, s, pyrim.-H), 3.67 (8H, m, morph.-H). (COOH proton was not observed, probably due to exchange with water in acetone-d_6). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 164.9$, 158.9, 158.5, 156.5, 112.7, 65.7, 43.9. IR ν_{max} (KBr): 1705 (COOH) cm^{-1}. Anal. calcd. for $C_9H_{10}ClN_3O_3$: C, 44.37; H, 4.14; N, 17.25. Found: C, 44.30; H, 4.26; N, 16.99.

2-(4-Carbamoylpiperidin-1-yl)-5-chloropyrimidine-4-carboxylic acid 5i. Yield (84%). Pale yellow crystals, mp 121.5–122.5°C (dec.). ^1H NMR (300 MHz, DMSO-d_6): $\delta = 13.90$ (1H, br. s, COOH), 8.45 (1H, s, pyrim. -H), 7.30 (1H, s, CONH), 6.82 (1H, s, CONH), 4.54 (1H, m, piper.-H), 2.93 (2H, m, piper.-H), 2.39 (2H, m, piper.-H), 1.80 (2H, m, piper.-H), 1.44 (2H, m, piper.-H). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 175.9$, 165.0, 158.8, 158. 5, 156.6, 111.9, 44.3, 41.4, 27.9. IR ν_{max} (KBr): 1715 (COOH) cm^{-1}. Anal. calcd. for $C_{11}H_{13}ClN_4O_3$: C, 46.41; H, 4.60; N, 19.68. Found: C, 46.59; H, 4.76; N, 19.70.

5-Chloro-2-(4-benzylpiperidin-1-yl)-pyrimidine-4-carboxylic acid 5j. Yield (54%). Pale yellow crystals, mp 111–112°C (dec.). ^1H NMR (100 MHz, acetone-d_6): $\delta = 8.43$ (1H, s, pyrim.-H), 7.34–7.1 (5H, m, Ar*H*), 5.20 (2H, m, CH_2Ph), 4.63 (2H, m, piper.-H), 2.90 (2H, m, piper.-H), 2.56 (2H, m, piper.-H), 1.77 (2H, m, piper.-H), 1.27 (1H, m, piper.-H). (COOH proton was not observed, probably due to exchange with water in acetone-d_6). IR ν_{max} (KBr): 1720 (COOH) cm^{-1}. Anal. calcd. for $C_{17}H_{18}ClN_3O_2$: C, 61.54; H, 5.47; N, 12.66. Found: C, 61.55; H, 5.21; N, 12.72.

2-(1-Azepanyl)-5-chloropyrimidine-4-carboxylic acid 5k. Yield (64%). Pale yellow crystals, mp 133.5–134.5°C (dec.). ^1H NMR (100 MHz, acetone-d_6): $\delta = 8.44$ (1H, s, pyrim.-H), 3.85–3.7 (4H, m, CH_2-N-CH_2), 1.90–1.45 (8H, m, -$(CH_2)_4$-). (COOH proton was not observed, probably due to exchange with water in acetone-d_6). IR ν_{max} (KBr): 1715 (COOH)

cm^{-1}. Anal. calcd. for $C_{11}H_{14}ClN_3O_2$: C, 51.67; H, 5.52; N, 16.43. Found: C, 51.54; H, 5.41; N, 16.12.

5-Bromo-2-(morpholin-4-yl)-pyrimidine-4-carboxylic acid 5l. Yield (76%). Pale yellow crystals, mp 131.5–132.5°C (dec.). ^{1}H NMR (100 MHz, acetone-d_6): $\delta = 8.56$ (1H, s, pyrim.-H), 3.74 (8H, m, morph.-H). (COOH proton was not observed, probably due to exchange with water in acetone-d_6). ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 164.9$, 158.9, 158.5, 156.5, 112.7, 65.7, 43.9. IR ν_{max} (KBr): 1705 (COOH) cm^{-1}. Anal. calcd. for $C_9H_{10}BrN_3O_3$: C, 37.52; H, 3.50; N, 14.59. Found.: C, 37.39; H, 3.34; N, 14.55.

Decarboxylation of Acids 6: General Procedure for Preparation of 2-Amino-5-chloropyrimidines 7a–c

To solution of corresponding 2-amino-5-chloro-pyrimidine-4-carboxylic acid **5** (2 mmol) in toluene (10 mL), tripropylamin (0.1 mL) was added. The mixture was refluxed for 30 min. After solvent evaporation, the product was obtained as a yellowish solid, which as shown by NMR and TLC, does not require further purification.

Data

Benzylamino-5-chloropyrimidine 7a. Yield (99%), mp 109°C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.36$ (2H, s, pyrim.-H), 7.41-7.23 (5H, m, Ar*H*), 6.70 (1H, d, *J* 6.2 Hz, NH), 4.62 (2H, d, *J* 6.2 Hz, -CH_2-NH). Anal. calcd. for $C_{11}H_{10}ClN_3$: C, 60.14; H, 4.59; N, 19.13. Found: C, 60.27; H, 4.55; N, 18.97.

5-Chloro-2-diethylaminopyrimidine 7b. Yield (99%). Yellowish crystals, mp 86°C. ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.37$ (2H, s, pyrim.-H), 3.65 (4H, q, *J* 7.3 Hz, CH_2CH_3), 1.17 (6H, t, *J* 7.3 Hz, CH_2CH_3). Anal. calcd. for $C_8H_{12}ClN_3$: C, 51.76; H, 6.52; N, 22.63. Found: C, 51.85; H, 6.79; N, 22.69.

5-Chloro-2-(piperidin-1-yl)-pyrimidine 7c. Yield (99%). Yellowish crystals, mp 96°C. ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.36$ (2H, s, pyrim.-H), 3.70 (4H, m, CH_2-N-CH_2), 1.63–1.49 [6H, 2 m, -$(CH_2)_3$-). ^{13}C NMR (125 MHz, DMSO-d_6): $\delta = 159.8$, 156.2, 117.0, 44.8, 25.5, 24.5. MS (EI) m/z (%): 197 (M^+) (100), 182 (49), 168 (73), 154 (44), 142 (25), 114 (32), 84 (19). Anal. calcd. for $C_8H_{12}ClN_3$: C, 54.69; H, 6.12; N, 21.26. Found: C, 54.75; H, 6.12; N, 21.41.

5-Chloro-2-(piperidin-1-yl)-pyrimidine-4-carboxylic acid chloride 8a. To a suspension of 5-chloro-2-(piperidin-1-yl)-pyrimidine-4-carboxylic acid

(**5g**) (2.41 g, 10 mmol) in benzene (20 mL), thionylchloride (2.38 g, 20 mmol) was added, and the mixture was refluxed for 2 h. After solvent evaporation, the product was obtained as a yellow solid, which was used in further transformations without purification. Yield 2.57 g (99%), mp 94–95°C. ^{1}H NMR (100 MHz, $CDCl_3$): $\delta = 8.42$ (1H, s, pyrim.-H), 3.87–3.73 (4H, m, CH_2-N-CH_2), 1.75–1.45 [6H, m, -$(CH_2)_3$-].

5-Chloro-2-(morpholin-4-yl)-pyrimidine-4-carboxylic acid chloride 8b. According to the procedure for **8a**, compound **8b** was obtained as a yellow solid. Yield (100%), mp 97–98°C. ^{1}H NMR (100 MHz, $CDCl_3$): $\delta = 8.43$ (1H, s, pyrim.-H), 3.80 (8H, m, morph.-H).

2-[5-Chloro-2-(piperidin-1-yl)-pyrimidin-4-yl]-2-oxo-1-(pyridin-2-yl)-propio-nitrile 4a. To a solution of pyridin-2-yl-acetonitrile **9** (240 mg, 2 mmol) and pyridine (2.2 mmol, 0.180 mL) in anhydrous dioxane (20 mL), **8a** (0.52 g, 2 mmol) was added. The reaction mixture was heated to 80–90°C for 1.5 h. After cooling, the solvent was removed in vacuo, and the residue was treated with water, filtered, dried, and recrystallized from dioxane to yield 0.65 g (95%) of **4a** as a yellow solid, mp 232–233°C. ^{1}H NMR (100 MHz, DMSO-d_6): $\delta = 15.4$ (1H, br. s, chelat.-H), 8.52 (1H, s, pyrim.-H), 8.49 (1H, br. t, α-pyridine-H), 8.25 (1H, ddd, J 8.8, 7.4, 1.5 Hz, γ-pyridine-H), 7.46 (1H, d, J 8.8 Hz, pyridine-H), 7.43 (1H, dd, J 7.4, 5.6 Hz, pyridine-H), 3.77-3.69 (4H, m, CH_2-N-CH_2), 1.75–1.45 [6H, m, -$(CH_2)_3$-]. IR ν_{max} (KBr): 2195 (CN) cm^{-1}. Anal. calcd. for $C_{17}H_{16}ClN_5O$: C, 59.74; H, 4.72; N, 20.49. Found: C, 59.71; H, 4.97; N, 20.61.

2-[5-Chloro-2-(morpholin-4-yl)-pyrimidin-4-yl]-2-oxo-1-(pyridin-2-yl)-propio-nitrile 4b. According to the procedure for **4a**, compound **4b** was obtained as a yellow solid. Yield (84%), mp 247–248°C. ^{1}H NMR (100 MHz, DMSO-d_6): $\delta = 15.40$ (1H, br. s, chelat.-H), 8.53 (1H, s, pyrim.-H), 8.49 (1H, br. t, α-pyridine-H), 8.25 (1H, ddd, J 8.8, 7.4, 1.5 Hz, γ-pyridine-H), 7.46 (1H, d, J 8.8 Hz, pyridine-H), 7.43 (1H, dd, J 7.4, 5.6 Hz, pyridine-H), 3.69 (8H, m, morph.-CH_2). IR ν_{max} (KBr): 2195 (CN) cm^{-1}. MS (EI) m/z (%): 343 (M^+) (98), 308 (100), 285 (76), 250 (16), 197 (14), 145 (55), 117 (21), 90 (16). Anal. calcd. for $C_{16}H_{14}ClN_5O_2$: C, 55.90; H, 4.10; N, 20.37. Found: C, 55.93; H, 4.15; N, 20.21.

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