Facile Synthesis of Some Novel Tetrasubstituted 2,4-Diaminopyrimidine Derivatives in Aqueous Glucose Solution as a Fully Green Medium and Promoter

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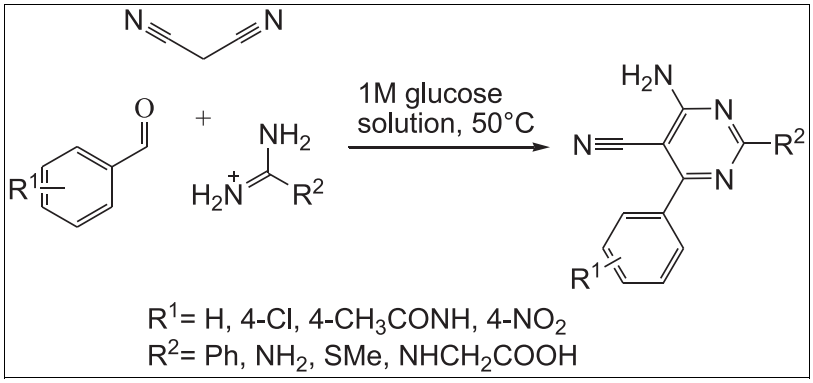

A novel environmentally benign method toward the synthesis of some novel tetrasubstituted 2,4-diaminopyrimidine derivatives using an aqueous glucose-mediated one-pot three-component reaction of malononitrile with various benzaldehyde and amidine derivatives is reported. Some pyrimidine derivatives possessing α-amino acid moiety were synthesized by the present protocol for the first time. This protocol offers advantages including facile reaction conditions, using naturally occurring glucose as promoter and water as solvent, simple work-up, relatively short reaction times, and high yields of the products.

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INTRODUCTION

Pyrimidine derivatives specially have contributed in the structure of many naturally occurring compounds such as heteromines (Fig. 1a), crambescins, and manzacidins [1]. Many pharmaceutically active ingredients such as antibiotics [2], antimalarials [3], selective A_3 adenosine receptor antagonists [4], and antiproliferative agents [5], and some novel specific radiotracers for positron emission tomography [6] have been designed and studied possessing this structural motif. Several valuable reviews are found illustrating the medicinal and therapeutic properties of pyrimidine derivatives [5,7,8]. Especially, pyrimidines having amino group at positions 2 and 4 of the ring have been reported to exhibit application in Alzheimer's disease treatment (Fig. 1b) [9].

Moreover, pyrimidine derivatives have played a significant role in agriculture as crop protection agents [10] and in electro-optics as building blocks for calamitic liquid crystals [11]. Accordingly, the endeavors toward introducing novel safer and more effective methods for the synthesis of this class of heterocycles starting from non-cyclic raw materials appear crucial and noteworthy. Recently, numerous synthetic methods have been reported in the literature for the synthesis of these valuable heterocycles through ring construction of linear starting materials. The most important strategy toward the synthesis of pyrimidine derivatives having 4-amino substituent includes the one-pot three-component reaction of malononitrile, aromatic aldehydes, and amidine derivatives using a basic catalyst [12–19]. Despite the fact that these methods all have their advantages, the use of basic catalyst mostly metal oxides seems necessary to promote the reaction. It appears that Lewis acidity of metal ion synergistically cooperates with oxidative and basic character of oxide anion in these cases. In addition, some of these methods are stepwise, and the other ones require high reaction temperatures and laborious purification of the products such as column chromatography.

In recent years, the development of multicomponent reactions is expanding remarkably as this protocol has been employed widely as a beneficial approach for the synthesis of many classes of heterocyclic building blocks. This is due to the fact that they play the role of alternatives to the stepwise construction of complex heterocyclic structures of importance for medicinal research. The most significant features of multicomponent synthetic strategies encompass characteristic terms such as atom economy, cost-effectiveness, and the product structure diversity [20,21].

Provided by environmental and social interests, the emphasis on providing novel and safer synthetic methodologies regarding the green chemistry principles has arisen as a very important area of research [22]. Recently, having shifted the emphasis of green chemistry fields of research toward engaging bio-based materials

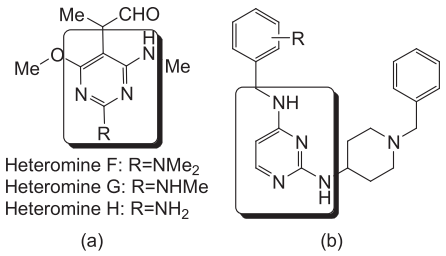


Figure 1. (a) The structures of three natural products having 2,4-diaminopyrimidine scaffold. (b) The structure of 2,4-diaminopyrimidine derivatives recently studied as a favorable template for Alzheimer's disease treatment.

with various structures, an important research challenge for green chemistry will also be retrieving the bio-based building blocks in order to fulfill this requirement [23]. Besides their biochemical significance, carbohydrates have played a much serious role in today's organic chemistry research as raw materials for the synthesis of various organic compounds as well [24,25]. Glucose, as one of the simple and straightforward polyhydroxy sugars, has been used as a ligand with modified structure for some synthetic and asymmetric catalysis purposes [26–28]. In addition, the aqueous glucose solution has been utilized as a novel polar and fully green reaction medium and promoter in the synthesis of 2,6-dioxohexahydropyrimidines through an isocyanide-based multicomponent reaction [29] and the synthesis of benzimidazoles through oxidant-free cyclodehydrogenation of aniline Schiff bases [30]. In continuation of our previous efforts toward the synthesis of pyrimidine derivatives and their fused analogs [31–34], and with a view of multicomponent reactions as powerful tool for the pursuit in molecular complexity and diversity [20,21], we herein wish to report a novel green methodology for the synthesis of four substituted 2,4-diaminopyrimidine-5-carbonitrile derivatives through a one-pot catalyst and oxidant-free three-component reaction of malononitrile with various benzaldehyde and amidine derivatives in aqueous glucose solution as medium and promoter. In the present study, we managed to synthesize some novel pyrimidine derivatives possessing an α-amino acid moiety at position 2 of the ring. The derivatives had not been obtained by previously reported methodologies.

RESULTS AND DISCUSSION

Our main goal was to develop a green protocol for the synthesis of some novel pyrimidine-5-carbonitrile derivatives bearing amino groups at positions 2 and 4 of the ring. With the aim of fulfilling the green chemistry requirement as our secondary objective, the application of aqueous glucose solution as medium and promoter was examined in the absence of extra catalyst and oxidant. The reaction of malononitrile (1 mmol), benzaldehyde (1 mmol), and benzamidine hydrochloride (1 mmol) was used as the model reaction. Various glucose concentrations, solvents, and reaction temperatures were scanned (Scheme 1), and the results are presented in Table 1.

Scheme 1. The model reaction for the synthesis of 4-aminopyrimidine-5-carbonitrile derivatives.

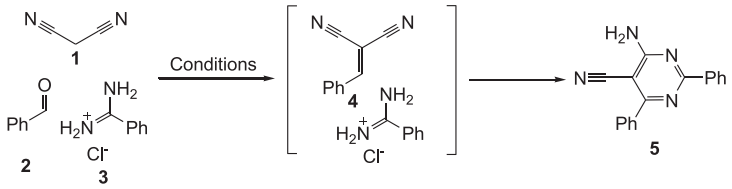


Table 1

Screening various reaction conditions for the aqueous glucose-mediated synthesis of 4-aminopyrimidine-5-carbonitrile derivatives[a].

Entry	Solvent	Glucose concentration (*M*)	Temperature[b] (°C)	Time (h)	Yield[c] (%)
1	H_2O	No glucose	50	12	No reaction
2	H_2O	1	25	12	No reaction
3	H_2O	1	50	2	94
4	H_2O	2	50	2	89
5	H_2O	3	50	2	90
6	H_2O	4	50	5	95
7	H_2O/EtOH (50:50)	1	25	12	47[d]
8	H_2O/EtOH (50:50)	1	50	7	33
9	H_2O/EtOH (50:50)	1	Reflux	5.5	42
10	H_2O/EtOH (50:50)	4	Reflux	8	31

[a]The reactions were carried out with 1 mmol of the reactants in 5 mL of the solvents specified.
[b]When performed at reflux in aqueous glucose solution, not only was observed no remarkable rate acceleration but also the yields reduced to some extent.
[c]Isolated products.
[d]Only benzylidene malononitrile (**4**) was formed (47%).

The results in Table 1 imply some important points. The model reaction did not proceed in pure water even at elevated temperatures. When compared with the other data, this observation represents the effect of glucose on the model reaction. The increasing glucose concentration in reaction medium did not have any enhancing effect on the yield and the reaction times. The reaction yield increased insignificantly, while the reaction rate decreased interestingly going from 1*M* to 4*M* glucose solution. The mixed solvent case (H_2O/EtOH) proceeded in a similar manner. The reaction rates and yields both decreased in this solvent system unexpectedly, while higher reaction yields and shorter reaction times were expected. Whereas only the benzylidene malononitrile intermediate 4 was formed at ambient temperatures, medium yields of the desired product were obtained at elevated temperatures (Table 1, entries 7–10). This could be due to the fact that in mixed solvent, the two reactants benzaldehyde and malononitrile dissolve in EtOH better than in water, whereas benzamidine hydrochloride does not dissolve in EtOH at all. This keeps the reactants apart from each other causing reaction failure. Besides in water as solvent containing glucose, the reactants are excluded from solvent bulk and aggregated to each other leading to faster reactions and higher yields of the product (see entries 7–10 in comparison with entries 2–6, Table 1). The reactions were performed very well at 50°C, and elevated temperatures did not seem necessary (Table 1, entries 3 to 6).

Regarding 1*M* aqueous glucose solution at 50°C as optimized conditions, the scope and generality of this protocol for the synthesis of novel 2,4-diaminopyrimidine derivatives were examined. Various benzaldehyde and amidine derivatives were utilized along with malononitrile under optimized reaction conditions. As stated before, an important aim of the present work was to introduce novel 2,4-diaminopyrimidine derivatives. In order to fulfill this purpose, four different amidine derivatives were applied in this protocol along with various benzaldehydes (Scheme 2).

The results are presented in Table 2. Pyrimidine-5-carbonitrile derivatives with diverse structural motifs on positions 2 and 6 were formed by using benzaldehyde derivatives with diverse electron demand and four unlike amidine derivatives. Good reactivities in terms of yields and reaction times were observed under the reaction conditions in 1*M* glucose solution. The reactions were accomplished within relatively short reaction times (1.5 to 5 h) with good to excellent product yields. Guanidinium carbonate was the most reactive amidine derivative according to observed reaction times and yields (entries 2, 10, and 11). Only when 4-nitrobenzaldehyde was used, a diminished reactivity with guanidinium carbonate was noticed. The electron donation did not show a notable impact on reaction rates and yields. A relatively small increment in reaction rates for 4-acetamidobenzaldehyde was observed (entries 6 and 10 versus entries 1 and 2). With isothiouronium iodide as the amidine source, the reactivities showed not much difference for benzaldehyde and 4-chlorobenzaldehyde (entries 4 and 7). The *N*-amidinoglycine represented slowest reactions providing pyrimidine derivatives as novel amino acid derivative with great yields. Again, no noticeable preference for electron donation and withdrawal was observed in this case. Moreover, the reaction products were easily purified by filtration and stirring in water for several minutes. In most cases, no extra purification such as recrystallization was needed. Finally, the insolubility of all products causes easy separation by precipitation from the reaction mixture.

Then, the model reaction was performed under N_2 inert atmosphere, and no desired product formed. Only benzylidene malononitrile intermediate was obtained under this condition. This implies that the aerobic oxidation by molecular oxygen is required for the complete formation of aromatic pyrimidine ring. The reusability of aqueous glucose solution was then examined. The glucose solution was recycled by filtration and used four times successfully in the model reaction without any obvious decrease in yield and increasing of the reaction times (Fig. 2).

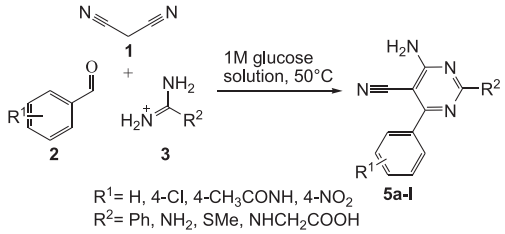
Table 2

The scope and generality of the aqueous glucose solution for the synthesis of 6-aryl-4-aminopyrimidine-5-carbonitrile derivatives[a].

Entry	R_1	R_2	Compound no.	Time (h)	Yield[b] (%)
1	H	Ph	**5a**	2	94
2	H	NH_2	**5b**	1.5	88
3	H	$NH\text{-}CH_2COOH$	**5c**	5	83
4	H	SMe	**5d**	4	87
5	4-Cl	Ph	**5e**	1.5	90
6	4-AcNH	Ph	**5f**	2	95
7	4-Cl	SMe	**5g**	3.5	84
8	4-Cl	$NH\text{-}CH_2COOH$	**5h**	4	81
9	$4\text{-}NO_2$	$NH\text{-}CH_2COOH$	**5i**	5	77
10	4-AcNH	NH_2	**5j**	1.5	92
11	4-Cl	NH_2	**5k**	2	86
12	$4\text{-}NO_2$	NH_2	**5l**	4	75

[a]1 mmol of each reactant was used in 5 mL 1*M* aqueous glucose solution.
[b]Isolated yield.

Scheme 2. The scope and generality of the present method for the aqueous glucose-mediated ecofriendly synthesis of pyrimidine-5-carbonitrile derivatives.



The reason for reaction progress in aqueous glucose solution as medium and promoter has not yet been investigated. A plausible mechanistic explanation is provided in Scheme 3. Probably, the polyhydroxy structure of glucose forms multiple hydrogen bonds to water molecules consecutively leading to a very polar reaction medium. This polarity may stimulate the reactants' dipole moments resulting in facilitating the reaction promotion. The carbonyl oxygen in aldehyde becomes more susceptible to nucleophilic attack by malononitrile (Scheme 3, State A). The resulting benzylidene malononitrile then undergoes a double nucleophilic attack by amidine through a cyclodehydrogenative process (Scheme 3, State B) to furnish the desired product.

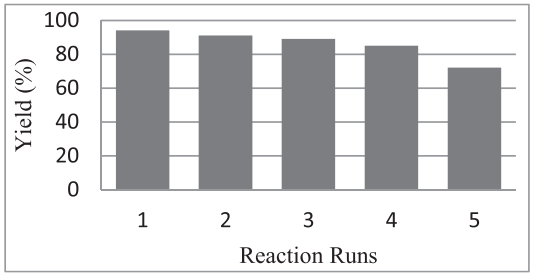


Figure 2. Examination of recyclability and reusability of aqueous glucose solution in the specified model reaction for the preparation of 2,4-diaminopyrimidine derivatives (reaction time 2 h).

Table 3 represents a comparative analysis for the present protocol relative to the previously reported important methods.

The data in Table 3 clearly indicate the preference of the present work over the previously reported methods. The common drawback of the previous methods is using metallic oxides as catalyst, which requires thorough work-up procedures to separate the products from the catalyst. Also, using metallic catalysts may result in the formation of toxic waste and is avoided according to green chemistry principles. The use of high temperatures and harmful organic solvents are the other most important drawbacks of the previous methods. While in the present study, the products are formed without using metallic catalysts and easily separated from the reaction mixture by a simple filtration with no need to laborious work-up. Lower reaction temperatures, comparable yields, using fully green reaction medium and promoter, and the synthesis of novel pyrimidine derivatives possessing amino acid moiety are the other advantages of the present protocol.

Scheme 3. A plausible mechanistic explanation for aqueous 1*M* glucose solution-mediated synthesis of pyrimidine-5-carbonitrile derivatives.

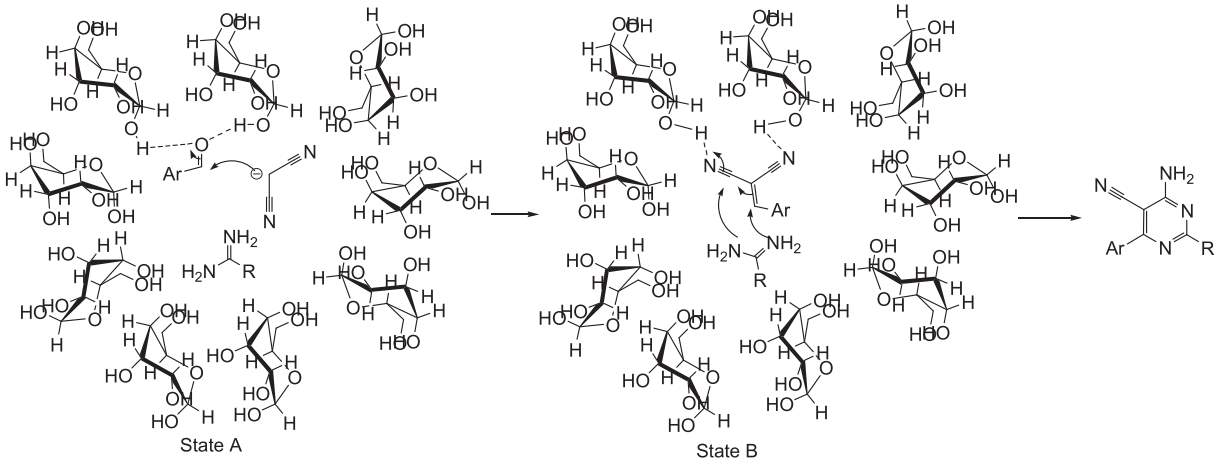


Table 3

Comparison of the present protocol results with some previously reported methods.

Entry	Solvent	Catalyst	Temperature	Time (h)	Yields (%)
Ref. [12]	CH_3CN	Nano MgO	Reflux	<1	70–96
Ref. [13]	H_2O	Nano ZnO	RT	<1	91–98
Ref. [15]	H_2O	Nano CuO	RT	<1	86–98
Ref. [17]	None	Nano Fe_3O_4	100°C	1–1.5	94–98
Ref. [19]	CH_3CN	$Bi(NO_3)_3.5H_2O$ and NEt_3	Reflux	<1	71–96
Present work	H_2O	Glucose	40–50°C	1.5–4	77–94

CONCLUSIONS

In summary, a novel safe and green methodology for the synthesis of some novel fully substituted pyrimidine-5-carbonitrile derivatives was reported through a one-pot three-component reaction of malononitrile, aromatic aldehydes and some amidine derivatives mediated by aqueous glucose solution. The reactions were carried out successfully at 50°C, and the products were simply isolated from the reaction mixture by vacuum filtration. The most important aspects of the present protocol include using a fully green and biocompatible glucose solution as medium and promoter, mild reaction conditions, good to excellent yields of the products, easy work-up, and the synthesis of derivatives having α-amino acid moiety for the first time. The pyrimidine derivatives having amino acid moiety are being studied for their possible bioactivities.

EXPERIMENTAL

Chemicals were purchased from Merck and Acros Organics companies (Merck Company, Hessen, Germany; Acros Organics Company, Geel, Belgium) and were used without further purification. Melting points were recorded on a KRUSS KSP-1N Serial No. 1306560 apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Bruker Tensor 27, type No. 121000 instrument (Bruker Optiks, Prague, Czech Republic). ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX-400 Avance spectrometer (Rheinstetten, Ettlingen, Germany) at 400 and 100 MHz using tetramethylsilane (TMS) as an internal standard. Chemical shifts (δ) are reported relative to TMS, and coupling constants (J) are reported in hertz (Hz). Mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer (Shimadzu Company, Tokyo, Japan) with 70eV ionization potential. Elemental analyses of new compounds were performed with a Vario EL III 0 serial no. 11024054 instrument (Elementar Analysensysteme GmbH, Hanau, Germany).

General procedure for the aqueous glucose solution-mediated three-component synthesis of pyrimidine-5-carbonitrile derivatives. A mixture of malononitrile (1.0 mmol), benzaldehyde derivative (1.0 mmol), and amidine derivative (1.2 mmol) was transferred into a reaction tube containing 5 mL 1*M* glucose solution and heated at 50°C for the specified reaction times. After completion of the reaction (monitored by TLC analysis, ethyl acetate/n-hexane mixtures), the reaction mixture was allowed to be cooled down to room temperature. Then, the precipitates were vacuum filtered off by a Büchi funnel and stirred in 10 mL water for 30 min in order to remove the glucose residues. The products were then filtered off and dried at ambient temperature and crystallized from ethanol/water mixtures whenever necessary to furnish the desired four substituted pyrimidine-5-carbonitrile derivatives.

Physical and spectroscopic data for 4-aminopyrimidine-5-carbonitrile derivatives. ***4-Amino-2,6-diphenylpyrimidine-5-carbonitrile (5a).*** mp 215°C (Lit. mp 212–213°C) [17]. IR (potassium bromide): 3393 (NH), 3278 (NH), 3079 (CH), 3052 (CH), 2219 (CN), 1603 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37–7.40 (m, 1H), 7.43 (d, J = 4.4 Hz, 4H), 7.46–7.48 (m, 2H), 7.56–7.59 (m, 3H), 7.77 (d, J = 5.4 Hz, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 80.21 (pyrimidine carbon bearing CN), 115.72 (CN), 126.39, 127.24, 128.11, 129.53, 130.28, 130.87, 132.30, 139.62, 162.89 (pyrimidine ring C), 165.68 (pyrimidine ring C), 168.78 (pyrimidine ring C) ppm.

2,4-Diamino-6-phenylpyrimidine-5-carbonitrile(5b). mp 232°C (Lit. mp 237–239°C) [14]. IR (potassium bromide): 3427 (NH), 3388 (NH), 3311 (NH), 3291 (NH), 3143, 3088, 2263 (CN), 1611 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.128 (bs, 4H), 7.37–7.40 (m, 1H), 7.47–7.50 (m, 3H), 7.74–7.77 (m, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.09 (pyrimidine carbon bearing CN), 114.67, 127.91, 130.18, 135.79, 140.47, 164.67 (pyrimidine ring C), 165.78 (pyrimidine ring C), 168.26 (pyrimidine ring C) ppm.

[(4-Amino-5-cyano-6-phenyl-2-pyrimidinyl)amino]acetic acid (5c). mp 201°C. IR (potassium bromide): 3461 (NH), 3385 (NH), 3311 (NH), 3089, 3063, 2912, 2279 (CN), 1597 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 2H, Aliphatic CH_2), 7.61–7.64 (m, 4H), 7.68–7.73 (m, 2H), 7.96 (d, J = 8.0 Hz, 2H), 8.57 (s, 1H), 11.56 (s, 1H, COOH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.2 (Aliphatic CH_2), 86.37 (pyrimidine carbon bearing CN), 114.88, 129.51, 129.90, 130.42, 134.28, 161.49 (pyrimidine ring C), 162.18 (pyrimidine ring C), 164.48 (pyrimidine ring C), 169.62 (COOH) ppm. MS (*m/z*): 269 (5), 211 (100), 141 (40), 179 (35). *Anal.* Calcd for $C_{13}H_{11}N_5O_2$: C, 57.99; H, 4.12; N, 26.01. Found: C, 58.21; H, 3.89; N, 25.77.

4-Amino-2-methylthio-6-phenylpyrimidine-5-carbonitrile (5d). mp 215°C (Lit. mp 210°C) [34]. IR (potassium bromide): 3453 (NH), 3387 (NH), 3203, 3162, 2911 (CH_3), 2303 (CN), 1591 (C=N) cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.51 (s, 3H, CH_3), 7.62 (t, J = 7.5 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.96 (d, J = 7.5 Hz, 2H), 8.28 (s, 1H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 15.89 (Aliphatic CH_3), 77.22 (pyrimidine carbon bearing CN), 128.67, 129.58, 130.72, 131.53, 134.61, 159.92 (pyrimidine ring C), 167.93 (pyrimidine ring C), 176.89 (pyrimidine ring C) ppm.

4-Amino-6-(4-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (5e). mp 219°C (Lit. mp 222°C) [17]. IR (potassium bromide): 3347, 3291, 3154, 3106, 2291, 1609 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.56 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.8 Hz, 2H), 7.95 (t, J = 8.4 Hz, 5H), 8.56 (s, 2H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ

79.87 (pyrimidine carbon bearing CN), 116.89 (CN), 127.33, 128.28, 129.38, 131.08, 132.23, 138.69, 139.77, 140.58, 163.23 (pyrimidine ring C), 165.11 (pyrimidine ring C), 169.43 (pyrimidine ring C) ppm.

6-(4-Acetamidophenyl)-4-amino-2-phenylpyrimidine-5-carbonitrile (5f). mp 250°C (245°C) [17]. IR (potassium bromide): 3383 (NH), 3342 (NH), 3167, 3087, 2936 (Aliphatic CH), 2291 (CN), 1616 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.11 (s, 3H, $COCH_3$), 7.52–7.57 (m, 3H), 7.78 (d, J = 8.4 Hz, 2H, Aromatic CH), 8.00 (d, J = 8.4 Hz, 2H, Aromatic CH), 8.39–8.43 (m, 2H), 10.3 (s, 1H, NHCO). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.08 (CH_3), 83.47 (pyrimidine carbon bearing CN), 116.59 (CN), 118.32, 128.41, 128.53, 129.49, 130.72, 131.47, 136.68, 141.83, 163.91 (pyrimidine ring C), 164.82 (pyrimidine ring C), 167.33 (pyrimidine ring C), 168.8 (C=O) ppm. MS (*m*/*z*): 329 (25), 271 (100), 198 (40), 194 (55).

4-Amino-6-(4-chlorophenyl)-2-methylthiopyrimidine-5-carbonitrile (5g). mp 221°C (Lit. mp 225) [32]. IR (potassium bromide): 3378 (NH), 3312 (NH), 3132 (Aromatic CH), 3099, 2911 (Aliphatic CH), 2311 (CN), 1622 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.52 (s, 3H, Aliphatic CH_3), 7.09 (s, 2H, NH_2), 7.69 (d, J = 7.9 Hz, 2H, Aromatic CH), 8.04 (d, J = 7.9 Hz, 2H, Aromatic CH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 13.47 (Aliphatic CH_3), 81.39 (pyrimidine carbon bearing CN), 116.58 (CN), 118.32, 129.33, 130.22, 141.88, 163.38 (pyrimidine ring C), 166.29 (pyrimidine ring C), 173.61 (pyrimidine ring C) ppm.

[(4-Amino-5-cyano-6-(4-chlorophenyl)-2-pyrimidinyl)amino]acetic acid (5h). mp 142°C. IR (potassium bromide): 3486 (NH), 3393 (NH), 3297, 3110, 2963 (CH), 2292 (CN), 1608 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.31 (s, 2H, CH_2), 6.95 (s, 2H), 7.73 (d, J = 8.8 Hz, 2H, Aromatic CH), 7.96 (d, J = 8.8 Hz, 2H, Aromatic CH), 8.56 (s, 1H), 11.76 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 39.17 (Aliphatic CH_2), 82.48 (pyrimidine carbon bearing CN), 115.69 (CN), 129.08, 135.77, 138.62, 141.21, 163.93 (pyrimidine ring C), 164.22 (pyrimidine ring C), 166.08 (pyrimidine ring C), 169.39 (COOH) ppm. MS (*m*/*z*): 303 (9), 244 (100), 175 (33), 128 (45). *Anal*. Calcd for $C_{13}H_{10}ClN_5O_2$: C, 51.41; H, 3.32; N, 23.06. Found: C, 51.09; H, 3.58; N, 23.33.

[(4-Amino-5-cyano-6-(4-nitrophenyl)-2-pyrimidinyl)amino] acetic acid (5i). mp 212°C. IR (KBr): 3491, 3401, 3309, 3205, 2979, 2303, 1616 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 3.42 (s, 2H, SCH_3), 7.03 (s, 2H, NH), 8.22 (d, J = 9.6 Hz, 2H, Aromatic CH), 8.47 (d, J = 9.6 Hz, 2H, Aromatic CH), 8.79 (s, 1H, NH), 12.07 (s, 1H, COOH). ^{13}C NMR (100 MHz, DMSO-d_6): δ 43.11 (SCH_3), 79.37 (pyrimidine carbon bearing CN), 116.92 (CN), 122.31, 138.28, 141.79, 143.57, 165.17 (pyrimidine ring C), 165.79 (pyrimidine ring C), 168.13 (pyrimidine ring C), 169.72 (COOH) ppm. MS (*m*/*z*): 314 (10), 255 (100), 187 (60), 129 (45). *Anal*. Calcd for $C_{13}H_{10}N_6O_4$: C, 49.69; H, 3.21; N, 26.74. Found: C, 49.83; H, 3.03; N, 26.51.

2,4-Diamino-6-(4-acetamidophenyl)pyrimidine-5-carbonitrile (5j). mp 240°C. IR (KBr): 3452 (NH), 3412 (NH), 3388 (NH), 3312 (NH), 3127, 2265 (CN), 1601 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 2.1 (s, 3H, $NHCOCH_3$), 7.11 (s, 2H, NH), 7.72 (d, J = 8.0 Hz, 2H, Aromatic CH), 7.83 (s, 2H, NH), 8.11 (d, J = 8.0 Hz, 2H, Aromatic CH), 8.8 (s, 1H, NHCO). ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.07 ($NHCOCH_3$), 71.12 (pyrimidine carbon bearing CN), 112.89 (CN), 117.28, 135.73, 139.15, 141.37, 164.09 (pyrimidine ring C), 164.78 (pyrimidine ring C), 166.32 (pyrimidine ring C), 167.23 (COOH) ppm. MS (*m*/*z*): 268 (22), 224 (100), 155 (55), 70 (40). *Anal*. Calcd for $C_{13}H_{12}N_6O$: C, 58.20; H, 4.51; N, 31.33. Found: C, 57.91; H, 4.83; N, 31.72.

2,4-Diamino-6-(4-chlorophenyl)pyrimidine-5-carbonitrile (5k). mp 259°C (Lit. mp 265–266°C) [14]. IR (potassium bromide): 3443 (NH), 3387 (NH), 3265 (NH), 3212 (NH), 3177, 3088, 2273 (CN), 1597 (C=N). ^1H NMR (400 MHz, DMSO-d_6): δ 6.86 (s, 2H, NH), 7.61 (d, J = 8.8 Hz, 2H, Aromatic CH), 7.83 (s, 2H, NH), 8.06 (d, J = 8.8 Hz, 2H, Aromatic CH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 77.36 (pyrimidine carbon bearing CN), 117.08 (CN), 127.93, 136.42, 139.46, 140.55, 163.69 (pyrimidine ring C), 165.73 (pyrimidine ring C), 170.34 (pyrimidine ring C) ppm.

2,4-Diamino-6-(4-nitrophenyl)pyrimidine-5-carbonitrile (5l). mp 261°C. IR (potassium bromide): 3497 (NH), 3423 (NH), 3387 (NH), 3319 (NH), 3277 (Aromatic CH), 3176 (Aromatic CH), 3062 (Aromatic CH), 2293 (CN), 1603 (C=N) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 7.17 (s, 2H, NH), 8.07 (d, J = 9.6 Hz, 2H, Aromatic CH), 8.31 (s, 2H, NH), 8.67 (d, J = 9.6 Hz, 2H, Aromatic CH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 74.67 (pyrimidine carbon bearing CN), 117.22 (CN), 121.18, 135.57, 138.21, 141.33, 163.48 (pyrimidine ring C), 165.13 (pyrimidine ring C), 171.88 (pyrimidine ring C) ppm. MS (*m*/*z*): 256 (20), 200 (60), 186 (100), 69 (70). *Anal*. Calcd for $C_{11}H_8N_6O_2$: C, 51.56; H, 3.15; N, 32.80. Found: C, 51.23; H, 3.44; N, 32.51.

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