A Facile Synthesis of New Pyrazolo[3,4-*d*]pyrimidine Derivatives *via* a One-Pot Four-Component Reaction with Sodium Acetate Supported on Basic Alumina as Promoter

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An efficient one-pot procedure for the synthesis of 3-amino-6-aryl-2-phenylpyrazolo[3,4-*d*]pyrimidine derivatives, through the reaction of aldehydes, malononitrile, benzamidine hydrochloride, and hydrazine hydrate in the presence of basic alumina-supported sodium acetate ($AcONa/Al_2O_3$) under reflux conditions, is reported. This protocol has some advantages, including the use of a simple and one-pot synthetic approach to attain pyrazolo[3,4-*d*]pyrimidine directly from four readily available starting materials, simple workup, high overall yields of the products, and the simultaneous conversion of a NO_2 to an amino group, offering an opportunity to synthesize more complex structures.

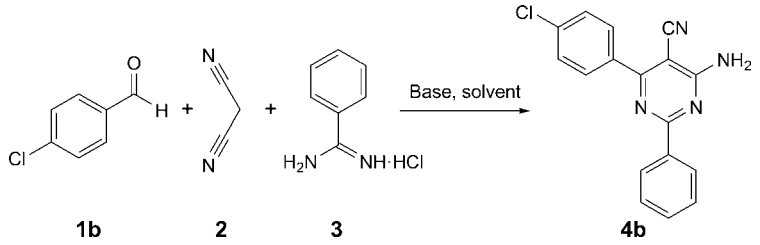
Introduction. – Fused pyrimidine derivatives have been shown to possess diverse biological activities, and among them, pyrazolo[3,4-*d*]pyrimidines as purine analogs have attracted considerable interest due to their remarkable pharmacological properties. These compounds were designed and synthesized as potent and selective kinase inhibitors [1], antileishmanial and antitrypanosomal [2], antibacterial [3], and antiviral agents [4], and adenosine A_{2A} receptor antagonists [5].

With these pharmacological profile of pyrazolo[3,4-*d*]pyrimidines, it seems beneficial to develop a more efficient synthetic route toward the synthesis of novel derivatives of this class of heterocycles. A literature survey provided information on methods used so far for the synthesis of pyrazolo-pyrimidines [6]. However, all these methods suffer from some drawbacks such as stepwise reaction conditions and tedious workup procedures.

Thus, the development of a simpler and more direct method for the preparation of pyrazolo-pyrimidines without one or more of these disadvantages appears to be crucial. Herein, we report a novel one-pot and multicomponent procedure for the synthesis of novel pyrazolo[3,4-*d*]pyrimidine derivatives directly through the reaction of aldehydes, malononitrile, benzamidine hydrochloride, and $NH_2NH_2 \cdot H_2O$ in the presence of basic alumina-supported sodium acetate, $AcONa/Al_2O_3$, as base.

Results and Discussion. – Initially, equimolar amounts of 4-chlorobenzaldehyde (**1b**), malononitrile (**2**), and benzamidine hydrochloride (**3**) were mixed and heated in different solvents and in the presence of various bases (*Scheme 1*).

Scheme 1. *Model Reaction Used for the Synthesis of Pyrimidine-5-carbonitrile Derivatives* (*e.g.* **4b**)



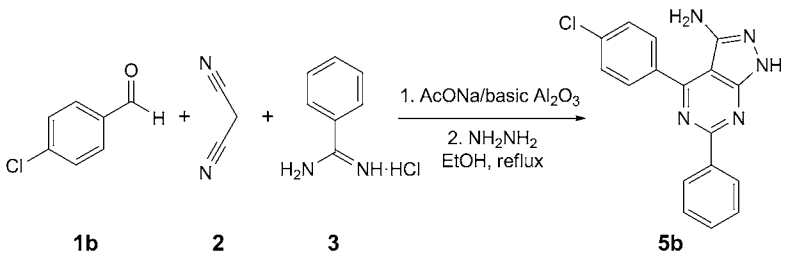
NaOH, Cs_2CO_3, ^{t}BuOK, CuO, Nano-MgO, AcONa, basic Al_2O_3, and AcONa/Al_2O_3 were examined as base in different solvents (EtOH, H_2O, BuOH, i-BuOH, i-PrOH, and no solvent at all).

The best results were obtained by using basic alumina-supported AcONa, CuO, and nano-MgO in EtOH as solvent under reflux condition.

To obtain the pyrazolo[3,4-*d*]pyrimidine derivatives, the process outlined in *Scheme 1* was repeated, however, this time in the presence of basic alumina-supported AcONa, followed by addition of 0.5 ml of $NH_2NH_2 \cdot H_2O$ to the reaction mixture after consumption of all reactants without separation of the formed pyrimidine product (*Scheme 2*). On the other hand, an unrecoverable dark-brown gum was formed in the case of using CuO and nano-MgO as base, in which TLC analysis did not show the formation of any new spot. In the case of basic alumina-supported AcONa as base, the reaction proceeded well in refluxing EtOH to form a new spot along with the disappearance of pyrimidine (*Scheme 2*). After aqueous workup, a pure pale-yellow solid was obtained. Full characterization of this compound was accomplished by spectroscopic methods (IR, ^{1}H-, and ^{13}C-NMR, and mass spectra).

The IR spectrum (KBr disc) of this compound revealed no CN absorption bond. In ^{1}H-NMR spectrum, we observed two different NH peaks at δ(H) 12.82 and 5.19 with signal-intensity ratio of 1:2, which can be attributed to the NH of pyrazolo ring and its amino group at C(3), respectively. Moreover, the mass spectrum showed a peak at *m*/*z* 321, which is compatible with 4-(4-chlorophenyl)-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-amine (**5b**). Elemental analysis and thorough interpretation of ^{13}C-NMR spectra also supported the formation of **5b** (*Scheme 2*).

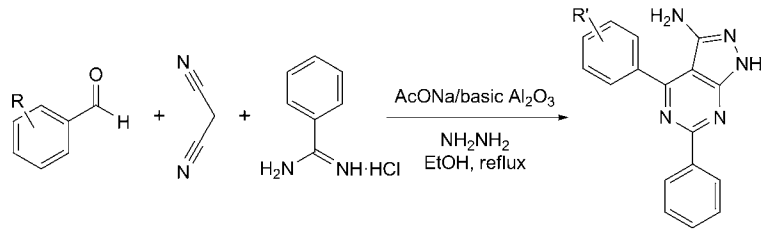
Scheme 2. *Model Reaction for the Synthesis of 4-(4-Chlorophenyl)-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-amines* (*e.g.* **5b**)



The reaction depicted in *Scheme 2* was also investigated under different base loadings, and the best results were obtained by using 0.1 g of basic alumina-supported AcONa. Increasing the amount of base did not affect the reaction time and yield.

To explore the scope and generality of this reaction, we have extended this process to various substituted benzaldehydes with malononitrile **2** and benzamidine hydrochloride **3**, in the presence of $NH_2NH_2 \cdot H_2O$. The reaction proceeded efficiently with various substituted benzaldehydes (*Table*).

Table. *Synthesis of* **5a**–**5j**, *by a One-Step Reaction, under Reflux Conditions*



1 **2** **3** **5a – 5j**

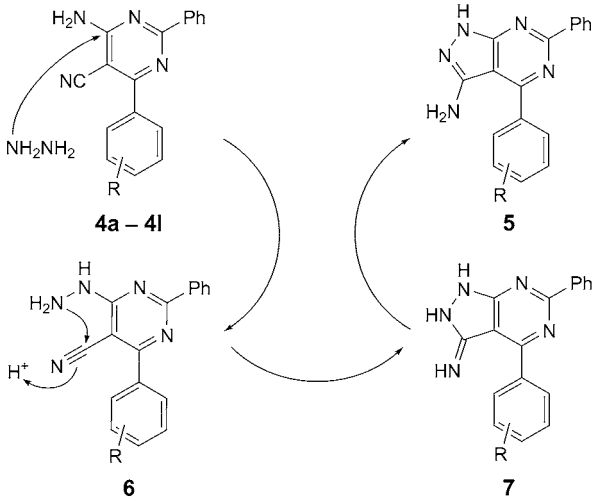
Entry	R	Product	R′	Time [h]	Yield [%][a])	M.p. [°]
1	H	**5a**	H	6	97	261–264
2	4-Cl	**5b**	4-Cl	8	95	267
3	2,3-Cl_2	**5c**	–	–	–	–
4	2-Cl	**5d**	2-Cl	2	98	212
5	4-CN	**5a**	H	6	85	261
6	4-Me	**5e**	4-Me	2	97	215
7	2,4-Cl_2	**5f**	–	–	–	–
8	3-NO_2	**5g**	3-NH_2	5	90	311
9	4-NO_2	**5h**	4-NH_2	5	88	223–229
10	1*H*-Indol-3-yl	**5i**	–	1	–	–
11	4-Acetamido	**5h**	4-NH_2	5	90	228–231
12	4-MeO	**5j**	4-MeO	8	95	211

[a]) Yield of isolated product.

When the pyrimidine derivatives with 4-(3-nitrophenyl), 4-(4-nitrophenyl), and 4-(4-acetamido) groups were used, the reaction led to the corresponding amino products (*Table*, *Entries 8*, *9*, and *11*) [7]. Similarly, when a pyrimidine derivative **4e** with a 4-(4-cyanophenyl) substituent (*cf. Scheme 1*) was used, we obtained again **5a**, *i.e.*, the H-atom replaced the CN group (*Table*, *Entry 5*) [8]. When bulky aryl substituents such as 2,3- and 2,4-dichlorophenyl (*Table*, *Entries 3*, *7*, and *10*) were at C(4) of the pyrimidine ring, the addition of $NH_2NH_2 \cdot H_2O$ led to the decomposition of the pyrimidine to the benzylidene malononitrile and benzamidine reactants rather than to the formation of the expected pyrazolo[3,4-*d*]pyrimidine derivatives.

A plausible mechanism for the formation of pyrazolo[3,4-*d*]pyrimidine derivatives is proposed in *Scheme 3*. First, NH_2NH_2 attacks C(6) of the pyrimidine ring as a nucleophile (*Scheme 3*). Then, the resulting hydrazino derivative **6** (this intermediate

Scheme 3. *Proposed Mechanism for the Formation of 4-Aryl-6-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-amines* **5** *Directly from Aldehydes, Malononitrile, Benzamidine Hydrochloride, and* $NH_2NH_2 \cdot H_2O$



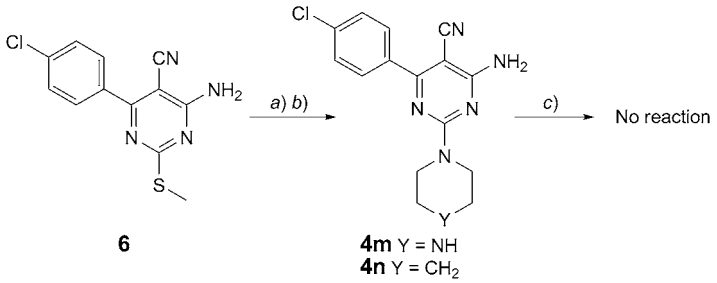
was isolated and characterized) intramolecularly undergoes the nucleophilic attack at the CN group leading to iminopyrazolo-pyrimidine **7**, which is transformed to the desired pyrazolo derivative **5** through aromatization.

Furthermore, considering that piperidine and piperazine are important structural motifs in a number of bioactive compounds, the potential of this protocol for the synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives containing such motifs was studied using two other pyrimidine derivatives with piperidine and piperazine substituents at C(2), *i.e.*, **4m** and **4n**, under the optimized reaction conditions (*Scheme 4*). For this purpose, 4-amino-6-(4-chlorophenyl)-2-(piperazin-1-yl)pyrimidine-5-carbonitrile (**4m**) and 4-amino-6-(4-chlorophenyl)-2-(piperidin-1-yl)pyrimidine-5-carbonitrile (**4n**) were prepared through a different synthetic pathway from 4-amino-6-(4-chlorophenyl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile (**8**) [9]. To our surprise, no reaction was observed between these two pyrimidine derivatives and $NH_2NH_2 \cdot H_2O$ in the presence of $AcONa/Al_2O_3$ in EtOH under reflux conditions (*Scheme 4*).

To find out why fused pyrimidine derivatives were not formed from the reaction between these pyrimidine derivatives and $NH_2NH_2 \cdot H_2O$, we investigated the effect of pyrimidine-ring substituents at C(2) by computational methods. In this context, DFT calculations, using Gaussian03w software package [10], were performed at B3LYP/6-31G* level of theory on the structures **A**, **B**, and **C** (*Fig. 1*).

The structures in *Fig. 1* were first drawn and fully optimized using GaussView 3.0 software and Gaussian03w software, respectively, at the above mentioned level of theory. The DFT calculations on the three pyrimidine derivatives supported the above mentioned experimental results. The computed lowest unoccupied molecular orbital (LUMO) of these three compounds elicited from the checkpoint files are depicted in *Fig. 2*.

Scheme 4. *Investigation of the Reaction of $NH_2NH_2 \cdot H_2O$ with 4-Amino-6-(4-chlorophenyl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile*



a) 1 mmol of 4-amino-6-(4-chlorophenyl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile, 3 mmol of *Oxone*, acetone/H_2O, r.t., overnight (quant.). *b*) Piperazine or piperidine (2 equiv.), dioxane, r.t., overnight. *c*) 1 mmol of **4m** or **4n**, AcONa/Al_2O_3 (0.1 g), NH_2NH_2 (0.5 ml), EtOH, reflux.

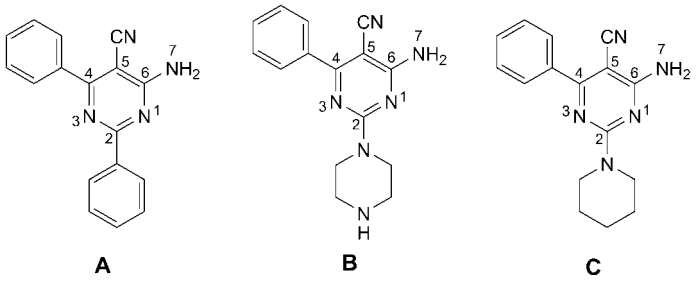


Fig. 1. *Pyrimidine derivatives selected for DFT calculations in the present study*

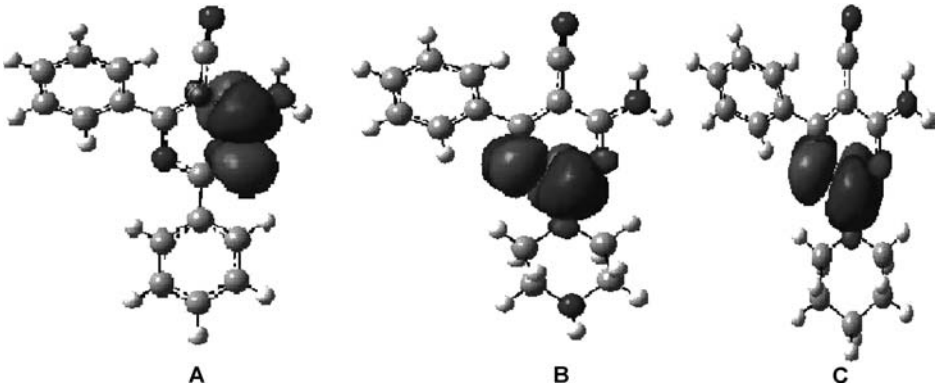


Fig. 2. *The optimized structures and LUMO molecular orbitals of compounds* **A**, **B**, *and* **C**

In the case of pyrimidine **A**, which possesses a Ph group at C(2), the LUMO is placed on C(6)–N(1), while for the other two, on C(2)–N(3) bond. This could imply that the most electrophilic C-atom would be C(6) in structure **A**, while C(2) would be

the most electrophilic one for the other two, *i.e.*, **B** and **C**. This means that hydrazine can attack the pyrimidine derivative **A** at C(6) of the ring in a nucleophilic manner, while the situation is different for compounds **B** and **C**, and these compounds would not undergo such a reaction at C(6). So, these results are in agreement with the observation that no pyrazolo-pyrimidine is formed from the reactions of pyrimidines **B** and **C**, and NH_2NH_2 under the optimized reaction conditions.

Conclusions. – In summary, we have developed a novel efficient protocol for the direct synthesis of fused pyrazolo[3,4-*d*]pyrimidine derivatives from the corresponding pyrimidine-5-carbonitriles. This protocol offers several advantages over the previously reported methods such as excellent yields of the products, simple workup, and straightforward synthesis of pyrazolo[3,4-*d*]pyrimidine derivatives *via* available starting materials. The simultaneous conversion of NO_2 to NH_2 group, which provides an opportunity to synthesize more complex structures by additional reaction steps, is a unique advantage of this protocol. We are attempting to expand this protocol to synthesis other heterocyclic building blocks.

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Experimental Part

General. M.p.: *Büchi B-540* apparatus. IR Spectra: *ABB Bomem* spectrometer Model *FTLA200–100* instrument. ^{1}H- and ^{13}C-NMR spectra: *Bruker DRX-300* spectrometer at 300 and 75 MHz, resp., with TMS as an internal standard; chemical shifts (δ) in ppm, and coupling constants (J) in Hz. MS: *Shimadzu QP 1100 EX* mass spectrometer with 70-eV ionization potential. Elemental analyses: *Vario EL III 0 Serial No. 11024054* instrument, results in agreement with calculated values.

Catalyst Preparation. AcONa (22 g, 0.27 mol) was poured into a flask containing H_2O (200 ml) and stirred for 4 min. Basic alumina (20 g, 0.19 mol) was then added gradually to this mixture while stirring, and the mixture was kept stirring for another 4 min. The resulting suspension was then dried *in vacuo*, and the solid residues were collected, dried at 110° for 24 h, and kept in well-closed container.

General Procedure for the Synthesis of **4a**–**4l**. Malononitrile (1 mmol), aldehyde (1 mmol), benzamidine hydrochloride (1 mmol), and AcONa/Al_2O_3 (0.1 g) in 5 ml of EtOH were mixed, heated under reflux, and the reaction was monitored by TLC (AcOEt/petroleum ether (PE) 1:2). After completion of the reaction, the mixture was cooled to r.t., filtered to separate the solid catalyst, and evaporated *in vacuo*. Then, the solid residues were washed with brine, and the org. solid was separated by filtration on a *Büchi* funnel and further purified by crystallization from EtOH to furnish the desired pyrimidine product.

4-Amino-2,6-diphenylpyrimidine-5-carbonitrile (**4a**). Yield: 266 mg (98%). White powder. M.p. 214° ([11]: 210–212°). IR: 3450, 3385, 2235. ^{1}H-NMR: 8.38–8.41 (*m*, 2 H); 7.95–7.98 (*m*, 2 H); 7.47–7.68 (*m*, 5 H); 7.47–7.68 (NH_2). ^{13}C-NMR: 168.1; 164.6; 164.0; 136.5; 131.5; 130.9; 128.6; 128.5; 128.4; 116.4; 84.4.

4-Amino-6-(4-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (**4b**). Yield: 293 mg (96%). Yellow powder. M.p. 222° ([11]: 222°). IR: 3450, 3390, 2237. ^{1}H-NMR: 8.37 (*d*, J = 6.2, 2 H); 7.99 (*d*, J = 8.5, 2 H); 7.64 (*d*, J = 8.5, 2 H); 7.48–7.57 (*m*, 3 H); 7.39 (NH_2). ^{13}C-NMR: 166.9; 164.5; 164.0; 136.4; 135.8; 135.3; 131.6; 130.5; 128.6; 128.5; 128.4; 116.2; 84.4.

4-Amino-6-(2,3-dichlorophenyl)-2-phenylpyrimidine-5-carbonitrile (**4c**). Yield: 326 mg (96%). Yellow powder. M.p. 231–234°. IR: 3473, 3388, 2235. ^{1}H-NMR: 8.29–8.31 (*m*, 3 H); 8.04 (*s*, NH_2); 7.82–7.85 (*m*, 1 H); 7.47–7.61 (*m*, 4 H). ^{13}C-NMR: 167.8; 164.3; 163.4; 138.3; 136.1; 132.2; 131.8; 129.3; 129.1; 128.6; 128.5; 114.9; 87.1. EI-MS: 340 (75), 342 (49), 317 (25), 315 (34), 312 (14), 311 (76), 310 (50), 309

(100), 308 (22), 307 (30), 282 (13), 280 (38), 239 (8), 237 (12), 206 (21), 198 (11), 189 (23), 166 (9), 164 (27), 104 (91), 77(35), 43 (14). Anal. calc. for $C_{17}H_{10}Cl_2N_4$ (341.19): C 59.84, H 2.95, N 16.42; found: C 59.33, H 2.91, N 17.10.

4-Amino-6-(2-chlorophenyl)-2-phenylpyrimidine-5-carbonitrile (**4d**). Yield: 290 mg (96%). Yellow powder. M.p. 200–202° ([12]: 196°). IR: 3475, 3390, 2235. ^{1}H-NMR: 8.31–8.34 (*m*, 2 H); 8.07–8.10 (*s*, NH_2); 7.58–7.65 (*m*, 3 H); 7.48–7.56 (*m*, 4 H). ^{13}C-NMR: 168.3; 164.2; 163.5; 136.3; 136.1; 131.7; 131.4; 131.0; 130.4; 129.7; 128.5; 128.4; 127.4; 115.1; 87.4.

4-Amino-6-(4-cyanophenyl)-2-phenylpyrimidine-5-carbonitrile (**4e**). Yield: 290 mg (98%). White powder. M.p. 299–300°. IR: 3475, 3390, 2220. ^{1}H-NMR: 8.36–8.39 (*m*, 2 H); 8.11–8.14 (*m*, 2 H); 8.05 (*d*, $J = 8.4$, 2 H); 7.48–7.56 (*m*, 3 H), 8.04–8.14 (NH_2). ^{13}C-NMR: 166.6; 164.3; 164.1; 140.7; 136.2; 132.4; 131.7; 129.5; 128.5; 128.4; 118.3; 115.8; 113.2; 85.0. EI-MS: 297 (100), 296 (60), 194 (92), 167 (18), 152 (11), 104 (53), 103 (201), 102 (12), 77 (28), 76 (19), 51 (14), 41 (7). Anal. calc. for $C_{18}H_{11}N_5$ (297.31): C 72.72, H 3.73, N 23.56; found: C 72.70, H 3.66, N 23.63.

4-Amino-6-(4-methylphenyl)-2-phenylpyrimidine-5-carbonitrile (**4f**). Yield: 326 mg (96%). White powder. M.p. 211° ([11]: 210°). IR: 3484, 3381, 2238. ^{1}H-NMR: 8.72–8.69 (*m*, 2 H); 8.40–8.37 (*m*, 2 H); 7.88 (*d*, $J = 9.0$, 2 H); 7.63 (*s*, NH_2); 7.50–7.54 (*m*, 3 H); 3.33 (*s*, 3 H). ^{13}C-NMR: 170.9; 167.9; 164.6; 143.3; 136.6; 135.4; 133.7; 132.6; 129.5; 128.5; 128.4; 116.5; 84.0; 21.2.

4-Amino-6-(2,4-dichlorophenyl)-2-phenylpyrimidine-5-carbonitrile (**4g**). Yield: 323 mg (96%). Yellow powder. M.p. 174° ([13]: 170–174°). IR: 3475, 3388, 2235. ^{1}H-NMR: 8.31 (*dd*, $J = 8.1$, 2 H); 7.94 (*s*, NH_2); 7.82 (*d*, $J = 1.7$, 1 H); 7.59–7.67 (*m*, 2 H); 7.39–7.53 (*m*, 3 H). ^{13}C-NMR: 167.3; 164.3; 163.4; 136.2; 135.3; 135.0; 132.3; 131.8; 131.7; 129.3; 128.5; 128.4; 127.7; 115.0; 87.4.

4-Amino-6-(3-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (**4h**). Yield: 303 mg (96%). Yellow powder. M.p. 201–202°. IR: 3455, 3385, 2230. ^{1}H-NMR: 8.75 (*s*, 1 H); 8.68–8.71 (*m*, 1 H); 8.37–8.52 (*m*, 3 H); 8.13 (*s*, NH_2); 7.86–7.91 (*m*, 1 H); 7.65–7.71 (*m*, 1 H); 7.52–7.54 (*m*, 2 H). ^{13}C-NMR: 165.9; 164.4; 164.1; 147.7; 137.9; 136.2; 135.0; 131.7; 130.3; 128.5; 128.4; 125.4; 123.3; 116.0; 84.9. EI-MS: 317 (84), 271 (59), 214 (56), 168 (67), 156 (100), 141 (91), 104 (71), 103 (72), 76 (72), 57 (45), 43 (44). Anal. calc. for $C_{17}H_{11}N_5O_2$ (317.30): C 64.35, H 3.49, N 22.07; found: C 64.35, H 3.33, N 22.28.

4-Amino-6-(4-nitrophenyl)-2-phenylpyrimidine-5-carbonitrile (**4i**). Yield: 304 mg (96%). Yellow powder. M.p. 215–217° ([12][14]: 215°). IR: 3455, 3388, 2228.,^{1}H-NMR: 8.65 (*d*, $J = 6.1$, 2 H); 8.52 (*d*, $J = 6.1$, 2 H); 8.00 (*s*, NH_2); 8.40–8.42 (*m*, 2 H); 7.43–7.52 (*m*, 3 H). ^{13}C-NMR: 170.2; 168.6; 160.8; 144.5; 140.4; 136.9; 130.2; 128.2; 127.1; 120.0; 116.0; 79.5.

*4-Amino-6-(1*H*-indol-3-yl)-2-phenylpyrimidine-5-carbonitrile* (**4j**). Yield: 280 mg (90%). Yellow powder. M.p. 230–232°. IR: 3450, 3385, 3315, 2222. ^{1}H-NMR: 12.68 (*s*, NH); 8.60 (*s*, 1 H); 8.49 (*s*, NH_2); 8.43 (*d*, $J = 6.2$, 2 H); 8.27 (*d*, $J = 9.0$, 1 H); 7.61–7.64 (*m*, 2 H); 7.51 (*d*, $J = 9.1$, 1 H); 7.39–7.42 (*m*, 3 H). ^{13}C-NMR: 177.2; 168.1; 162.5; 136.1; 133.1; 126.6; 123.8; 122.4; 118.9; 115.9; 115.8; 112.9; 110.9; 69.2. EI-MS: 311 (6), 208 (16), 194 (28), 193 (100), 166 (61), 165 (39), 142 (29), 138 (24), 88 (18), 63 (15), 51 (12). Anal. calc. for $C_{19}H_{13}N_5$ (311.34): C 73.30, H 4.21, N 22.49; found: C 72.55, H 4.93, N 22.52.

N-*[4-(6-Amino-5-cyano-2-phenylpyrimidin-4-yl)phenyl]acetamide* (**4k**). Yield: 326 mg (95%). Pale-yellow powder. M.p. 245° ([14]: 243–244°). IR: 3488, 3387, 3323, 2232, 1665. ^{1}H-NMR: 10.25 (*s*, NH); 8.40 (*d*, $J = 6.1$, 2 H); 7.99 (*d*, $J = 9.2$, 2 H); 7.89 (*s*, NH_2); 7.77 (*d*, $J = 9.2$, 2 H); 7.50–7.52 (*m*, 3 H); 2.1 (*s*, 3 H). ^{13}C-NMR: 168.7; 167.1; 164.7; 163.8; 141.8; 136.6; 131.4; 130.7; 129.4; 128.5; 128.4; 118.3; 116.7; 83.5; 24.1.

4-Amino-6-(4-methoxyphenyl)-2-phenylpyrimidine-5-carbonitrile (**4l**). Yield: 286 mg (95%). Pale-yellow powder. M.p. 213° ([11]: 213°). IR: 3490, 3388, 2238. ^{1}H-NMR: 8.38–8.41 (*m*, 2 H); 8.01 (*d*, $J = 9.1$, 2 H); 7.87 (*s*, NH_2); 7.50–7.52 (*m*, 3 H); 7.10 (*d*, $J = 9.1$, 2 H); 3.84 (*s*, 3 H). ^{13}C-NMR: 167.1; 164.7; 163.7; 161.5; 136.6; 131.4; 130.3; 128.6; 128.4; 128.3; 116.7; 113.8; 83.3; 55.3.

General Procedure for the Synthesis of **5a**–**5j**. Malononitrile (1 mmol), aldehyde (1 mmol), benzamidine hydrochloride (1 mmol), and $AcONa/Al_2O_3$ (0.1 g) in 5 ml of EtOH were mixed, refluxed for the specified time, and the reaction was monitored by TLC (AcOEt/PE 1:2). After completion of the reaction, $NH_2NH_2 \cdot H_2O$ (0.5 ml) was added to the mixture, and the mixture was again refluxed. After completion of the reaction, the mixture was cooled, and the solid catalyst was separated by filtration. Then, H_2O was added (10 ml) to the filtrate, and the solid residues were filtered and further recrystallized from EtOH.

*4,6-Diphenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5a**). Yield: 278 mg (97%). White powder. M.p. 261–264°. IR: 3432, 3329, 3301. ^{1}H-NMR: 12.78 (*s*, NH); 8.48–8.51 (*m*, 2 H); 7.99–8.02 (*m*, 2 H); 7.61–7.63 (*m*, 3 H); 7.51–7.53 (*m*, 3 H); 5.08 (NH_2). ^{13}C-NMR: 161.1; 160.0; 156.0; 147.7; 137.7; 137.3; 130.5; 130.4; 129.1; 128.8; 128.5; 128.0; 100.7. EI-MS: 286 (100), 258 (4), 167 (7), 155 (6), 149 (19), 128 (13), 104 (12), 77 (16), 58 (10), 43 (4), 41 (3). Anal. calc. for $C_{17}H_{13}N_5$ (287.32): C 71.06, H 4.56, N 24.37; found: C 70.92, H 4.61, N 24.45.

*4-(4-Chlorophenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5b**). Yield: 304 mg (95%). Pale-yellow powder. M.p. 267°. IR: 3449, 3325, 3307. ^{1}H-NMR: 12.82 (*s*, NH); 8.48–8.49 (*m*, 2 H); 8.05 (*d*, *J* = 8.3, 2 H); 7.67 (*d*, *J* = 8.3, 2 H); 7.51–7.53 (*m*, 3 H); 5.19 (NH_2). ^{13}C-NMR: 159.9; 159.8; 156.1; 147.8; 137.6; 136.0; 135.3; 131.2; 130.6; 128.8; 128.6; 128.1; 100.7. EI-MS: 321 (54), 258 (4), 167 (30), 149 (72), 145 (14), 136 (13), 135 (100), 117 (22), 113 (13), 111 (17), 105 (85), 97 (26), 77 (44), 71 (33), 69 (31), 57 (48), 55 (38), 43 (39), 41 (25). Anal. calc. for $C_{17}H_{12}ClN_5$ (321.76): C 63.46, H 3.76, N 21.77; found: C 63.58, H 3.75, N 21.65.

*4-(2-Chlorophenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5d**). Yield: 314 mg (98%). Pale-yellow powder. M.p. 212°. IR: 3445, 3328, 3310. ^{1}H-NMR: 12.79 (*s*, NH); 8.42–8.49 (*m*, 2 H); 7.50–7.67 (*m*, 7 H); 4.79 (NH_2). ^{13}C-NMR: 160.3; 159.2; 155.3; 147.6; 137.5; 135.5; 131.2; 130.7; 130.6; 130.0; 129.1; 128.7; 128.5; 128.1; 127.5; 102.2. EI-MS: 321 (100), 320 (39), 287 (37), 286 (61), 276 (12), 139 (29), 128 (14), 127 (19), 126 (16), 104 (30), 103 (13), 77 (37), 76 (17), 55 (14), 51 (16), 43 (15). Anal. calc. for $C_{17}H_{12}ClN_5$ (321.76): C 63.46, H 3.76, N 21.77; found: C 63.43, H 3.72, N 21.75.

*4-(4-Methylphenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5e**). Yield: 291 mg (97%). White powder. M.p. 215°. IR: 3433, 3320, 3303. ^{1}H-NMR: 12.75 (*s*, NH); 8.49 (*d*, *J* = 7.6, 2 H); 7.51–7.52 (*m*, 3 H); 7.42 (*d*, *J* = 7.7, 2 H); 5.08 (*s*, NH_2); 2.42 (*s*, 3 H). ^{13}C-NMR: 161.1; 160.0; 156.1; 147.7; 140.2; 137.7; 134.5; 130.4; 129.3; 129.1; 128.5; 128.0; 100.6; 21.0. EI-MS: 301 (100), 287 (20), 221 (11), 199 (20), 139 (35), 104 (63), 97 (20), 83 (42), 77 (53), 76 (32), 71 (12), 69 (22), 55 (48), 43 (52), 41 (15). Anal. calc. for $C_{18}H_{15}N_5$ (301.35): C 71.74, H 5.02, N 23.24; found: C 71.98, H 5.13, N 22.90.

*4-(3-Aminophenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5g**). Yield: 271 mg (90%). Pale-yellow powder. M.p. 311.5°. IR: 3430, 3416, 3341. ^{1}H-NMR: 12.00 (*s*, NH); 8.47–8.50 (*m*, 2 H); 7.50–7.52 (*m*, 3 H); 7.23–7.28 (*m*, 1 H); 7.13 (*s*, 1 H); 7.01 (*d*, *J* = 7.5, 1 H); 6.78 (*d*, *J* = 7.4, 1 H); 5.42 (*s*, NH_2); 5.09 (NH_2). ^{13}C-NMR: 162.1; 160.0; 155.8; 149.2; 147.6; 138.0; 137.7; 130.4; 129.3; 128.5; 128.0; 116.1; 115.7; 113.7;100.4. EI-MS: 302 (100), 301 (64), 288 (15), 287 (69), 286 (17), 272 (25), 184 (15), 183 (17), 142 (18), 104 (24), 103 (14), 77 (25), 43 (18). Anal. calc. for $C_{17}H_{14}N_6$ (302.33): C 67.54, H 4.67, N 27.80; found: C 67.47, H 4.56, N 28.18.

*4-(4-Aminophenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5h**). Yield: 265 mg (88%). Yellow powder. M.p. 223–229°. IR: 3432, 3416, 3338. ^{1}H-NMR: 12.58 (*s*, NH); 8.47–8.50 (*m*, 2 H); 7.83 (*d*, *J* = 8.4, 2 H); 7.49–7.51 (*m*, 3 H); 6.74 (*d*, *J* = 8.4, 2 H); 5.78 (*s*, NH_2); 5.07 (NH_2). ^{13}C-NMR: 161.3; 159.6; 156.3; 151.5; 147.8; 138.1; 130.8; 130.2; 128.4; 127.9; 124.1; 113.4; 99.6. EI-MS: 302 (87), 301 (100), 210 (14), 143 (23), 142 (24), 104 (38), 103 (17), 77 (26), 76 (13), 65 (14), 51 (7), 43 (5). Anal. calc. for $C_{17}H_{14}N_6$ (302.33): C 67.54, H 4.67, N 27.80; found: C 67.61, H 4.66, N 27.72.

*4-(4-Methoxyphenyl)-6-phenyl-1*H-*pyrazolo[3,4-*d*]pyrimidin-3-amine* (**5j**). Yield: 301 mg (95%). White powder. M.p. 213°. [14]: 211°. IR: 3432, 3414, 3300. ^{1}H-NMR: 8.47–8.49 (*m*, 2 H); 8.36–8.39 (*s*, NH); 8.01 (*d*, *J* = 8.5, 2 H); 7.49–7.51 (*m*, 3 H); 7.15 (*d*, *J* = 8.5, 2 H); 5.11 (*s*, NH_2); 3.85 (*s*, 3 H). ^{13}C-NMR: 161.2; 160.7; 159.9; 156.1; 147.8; 137.8; 137.8; 131.0; 130.4; 129.6; 128.5; 128.0; 114.2; 100.3; 55.3. EI-MS: 317 (79), 316 (60), 302 (38), 301 (20), 221 (17), 199 (26), 157 (14), 139 (22), 123 (14), 114 (33), 104 (83), 103 (30), 102 (20), 97 (25), 91 (20), 85 (20), 83 (33), 81 (20), 77 (70), 76 (36), 71 (28), 69 (51), 67 (27), 57 (51), 55 (68), 51 (27), 43 (100), 41 (49). Anal. calc. for $C_{18}H_{15}N_5O$ (317.34): C 68.13, H 4.76, N 22.07; found: C 68.41, H 4.66, N 22.11.

General Procedure for the Synthesis of **4m** *and* **4n**. To a soln. of 4-amino-6-(4-chlorophenyl)-2-(methylsulfanyl)pyrimidine-5-carbonitrile (1 mmol) in 5 ml of acetone was added *Oxone* (3 mmol) in 15 ml of H_2O at r.t., and the mixture was stirred overnight. After completion of the reaction, the solvent was evaporated, and the precipitates were dissolved in 5 ml of 1,4-dioxane, and piperazine or piperidine (2 mmol) was added to the mixture, which was stirred overnight. After completion (monitored by TLC (AcOEt/MeOH 10:1)), solvent was evaporated, and the solid residues were washed with H_2O and separated by filtration to obtain **4m** and **4n** as pale-yellow solids.

4-Amino-6-(4-chlorophenyl)-2-(piperazin-1-yl)pyrimidine-5-carbonitrile (**4m**). Yield: 292 mg (93%). Pale-yellow powder. M.p. 207°. IR: 3491, 3358, 2202. ^{1}H-NMR: 7.90 (*d*, *J* = 8.5, 2 H); 7.84 (*d*, *J* = 8.5, 2 H); 7.08 (*s*, NH, NH_2); 3.49–3.68 (*m*, 2 H); 2.88–3.01 (*m*, 2 H). ^{13}C-NMR: 44.5; 45.2; 85.6; 116.3; 128.9; 136.8; 137.6; 140.0; 164.3; 165.7; 170.9. EI-MS: 314 (10), 272 (30), 258 (34), 246 (55), 229 (24), 187 (21), 111 (15), 85 (16), 75 (18), 68 (24), 56 (100). Anal. calc. for $C_{15}H_{15}ClN_6$ (314.77): C 57.24, H 4.80, Cl 11.26, N 26.70; found: C 57.11, H 4.92, N 26.81.

4-Amino-6-(4-chlorophenyl)-2-(piperidin-1-yl)pyrimidine-5-carbonitrile (**4n**). Yield: 303 mg (97%). Pale-yellow powder. M.p. 183–185°. IR: 3491, 3347, 2202. ^{1}H-NMR: 8.88 (*s*, NH_2); 7.88 (*d*, *J* = 8.5, 2 H); 7.80 (*d*, *J* = 8.5, 2 H); 3.49–3.61 (*m*, 4 H); 1.48–1.59 (*m*, 3 H). ^{13}C-NMR: 24.5; 25.2; 46.6; 83.4; 116.4; 128.3; 136.9; 137.4; 140.8; 164.6; 165.1; 171.2. EI-MS: 313 (100), 284 (63), 258 (25), 229 (23), 195 (11), 84 (66), 55 (21). Anal. calc. for $C_{16}H_{16}ClN_5$ (313.78): C 61.24, H 5.14, N 22.32; found: C 61.35, H 5.12, N 22.48.

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