JOC The Journal of Organic Chemistry

Article

One-Pot Acid-promoted Synthesis of 6-Aminopyrazolopyrimidines from 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines or 5-Amino-1*H*-pyrazole-4-carbaldehydes with Cyanamide

Ching-Chun Tseng, Shuo-En Tsai, Sin-Min Li, and Fung Fuh Wong

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.9b02653 • Publication Date (Web): 18 Nov 2019

One-Pot Acid-promoted Synthesis of 6-Aminopyrazolopyrimidines from 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines or 5-Amino-1*H*-pyrazole-4-carbaldehydes with Cyanamide

Ching-Chun Tseng,[†,‡] Shuo-En Tsai,[†,‡] Sin-Min Li,[§] Fung Fuh Wong[†,*]

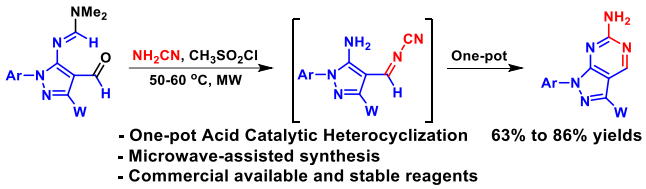
[†]*School of Pharmacy, China Medical University, No. 91, Hsueh-Shih Rd., Taichung, 40402, Taiwan*

[‡]*Ph.D. Program for Biotech Pharmaceutical Industry, China Medical University, No. 91, Hsueh-Shih Rd., Taichung, 40402, Taiwan*

[§]*Master Program for Pharmaceutical Manufacture, China Medical University, No. 91, Hsueh-Shih Rd., Taichung 40402, Taiwan*

*Corresponding author. Tel.: +886 4 2205 3366 ext. 5603; Fax: +886 4 2207 8083. E-mail address: wongfungfuh@yahoo.com.tw, ffwong@mail.cmu.edu.tw (F. F. Wong).

Key words: 6-Aminopyrazolo[3,4-*d*]pyrimidines, Pyrazolopyrimidines, Cyanamide, Formamidines, Heterocyclization, Microwave-assisted synthesis



ABSTRACT: A convenient and efficient one-pot acid-promoted synthesis of 6-aminopyrazolo[3,4-*d*]pyrimidine has been developed by treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines or 5-amino-1*H*-pyrazole-4-carbaldehydes with cyanamide ($NH_2C{\equiv}N$) in an acid-mediated solution. This synthetic route involves four steps of deprotection, imination, the key acid-promoted heterocyclization, and aromatization. Based on optimized studies, methanesulfonyl chloride is considered to be the best solvent. Furthermore, the microwave-assisted synthetic technique was also carried out to improve the major product 6-aminopyrazolo[3,4-*d*]pyrimidines in this method.

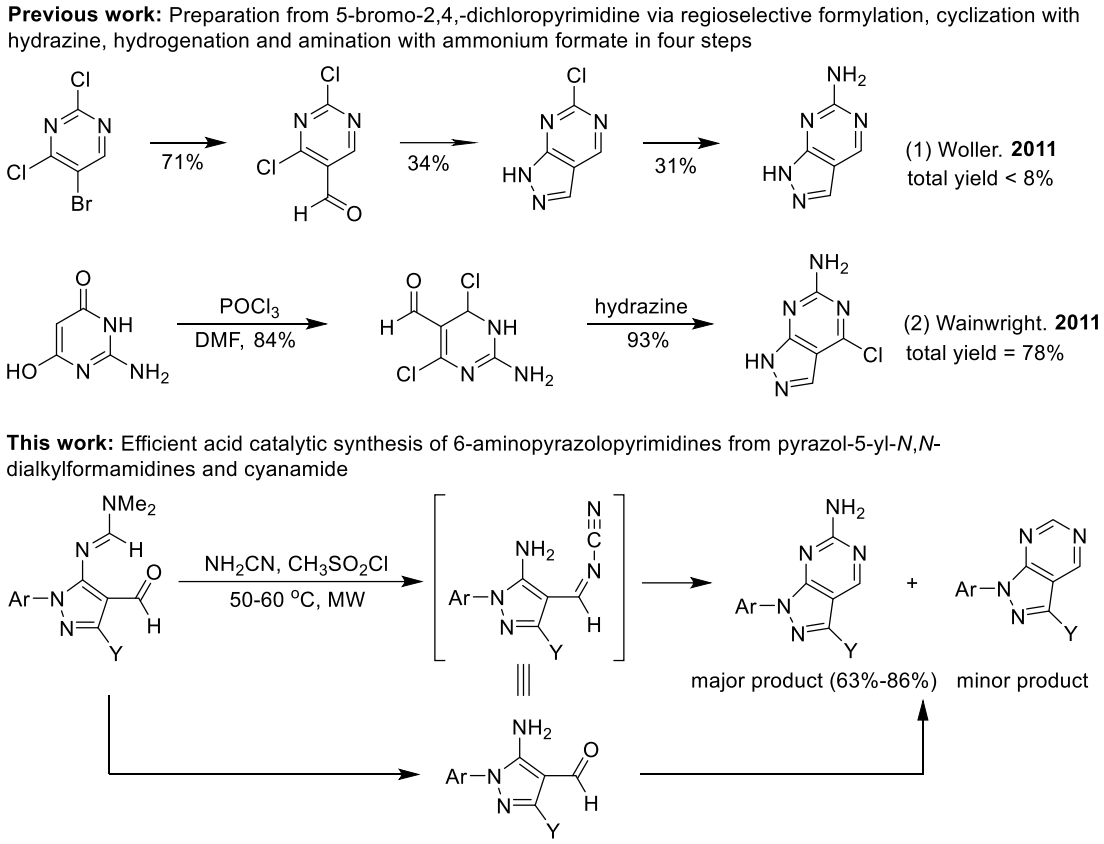
Moreover, our proposed mechanism was confirmed in this study, which demonstrates that *N*-[(5-amino-1,3-diaryl-1*H*-pyrazol-4-yl)methylene]cyanamide is the intermediate.

INTRODUCTION

Pyrazolo[3,4-*d*]pyrimidines are important bioactive heterocyclic molecules that have attracted attention as potential drugs or molecular tools.[1-10,14] In particular, 6-aminopyrazolo[3,4-*d*]pyrimidine analogs exhibit pharmacological activities; for example, inhibition of multiple-mitotic kinase (MMK),[11] of human epidermal growth factor receptor (EGFR) tyrosine kinase,[12] phosphodiesterase,[13] as well as anti-inflammat,[14] and cytotoxic activity.[15] Moreover, 6-aminopyrazolo[3,4-*d*]pyrimidines have demonstrated their antitumor activity by targeting Aurora kinases involved in mitosis.[11,16-18] Several methods are available for the preparation of 6-aminopyrazolo[3,4-*d*]pyrimidines.[18] Well-established synthetic strategies involve the regioselective formylation of 5-bromo-2,4,-dichloropyrimidine with morpholine-4-carbaldehyde, substitution and cyclization with hydrazine, as well as hydrogenation and amination with ammonium formate in the presence of palladium catalyst ((1) of Scheme 1). However, this synthetic pathway is complicated and cannot provide satisfactory yields. Wainwright et al. have simultaneously developed a more satisfactory procedure that uses 2-amino-4,6-dihydroxypyrimidine as starting material, whereby the formylation and chlorination with Vilsmeier reagent ($POCl_3$/DMF) and cyclization with hydrazine provides a 78% yield in two steps ((2) of Scheme 1).[19] Based on this observation, we aimed to develop a convenient and efficient acid-promoted method for synthesis of 6-aminopyrazolo[3,4-*d*]pyrimidines, by treating 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines with cyanamide ($NH_2C{\equiv}N$)[20] in the presence of an acid-mediated solvent (Scheme 1). In comparison with the

method described by Wainwright et al., our isolated yields and material costs are similar. However, our procedure is simpler and more direct.

Scheme 1. **Synthesis Routes of 6-Aminopyrazolo[3,4-*d*]pyrimidines**



Functional cyanamide ($NH_2C{\equiv}N$) can be used to produce different functional group transformations, including the conversion of cyanamide to carbodiimide,[21] dicyandiamide,[22] guanidines,[23] sulflimines,[24] urea,[25] thiourea,[26] and selenazadiphospholaminediselenides,[27] etc. Several modified cyanamides act as the electrophilic cyanating agent towards carbon, nitrogen, oxygen, and sulfur nucleophiles.[28] They also serve as readily available intermediates or versatile precursors for the synthesis of many natural and biologically active heterocyclic compounds, including 2-aminoimidazoles,[29] 1-substituted tetrazoles,[30] 1,3-diazepanes,[31] 3,4-dihydropyrimidin-2-ones,[32] 1,2,4-benzotriazine 1,4-dioxide,[33] melamine,[34] and *N*-alkyl or *N*-aryl imides[35] etc. Therefore, we examined cyanamide ($NH_2C{\equiv}N$) as an alternative aminating reagent and its reaction towards

1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine under the acidic condition. Our results indicated that methanesulfonyl chloride is the best acidic solution. We also found that the microwave-assisted technique markedly promoted the formation of 6-aminopyrazolo[3,4-*d*]pyrimidines as major products (Scheme 1).

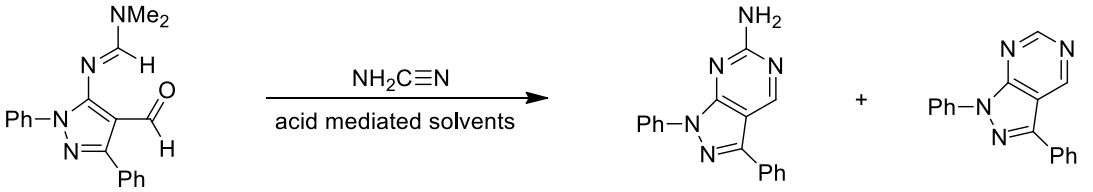
RESULTS AND DISCUSSION

Cyanamide has been widely used as an intermediate for preparation of many heterocyclic compounds. Therefore, we evaluated a method for synthesis of 6-aminopyrazolo[3,4-*d*]pyrimidines by reacting 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine with cyanamide ($NH_2C{\equiv}N$) as the aminating agent under acidic conditions. Initially, we investigated the possibility of the amination cyclization reaction of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1** with $NH_2C{\equiv}N$ under different acid-mediated solvents, such as conc. HCl, $HCl_{(aq)}$/AcOH co-solvent, acetic acid (AcOH), trifluoroacetic acid (TFA), methanesulfonic acid,[36] methanesulfonylchloride, and *p*-toluenesulfonylchloride.

The initial solvent investigation used the typical amination cyclization to synthesize 6-aminopyrazolo[3,4-*d*]pyrimidine, by reacting the model starting material 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** with 3.0 equivalent of cyanamide ($NH_2C{\equiv}N$) in the presence of an aqueous acid-mediated solvent solution including aqueous conc. HCl and $HCl_{(aq)}$/AcOH co-solvent (2.0 mL) at reflux for 3 h. Pyrazolo[3,4-*d*]pyrimidine product **3a** was revealed to be the major product in 48% to 62% yields without the expected 6-aminopyrazolo[3,4-*d*]pyrimidine product **2a** (Table 1, entries 1–3). The screening of acetic acid (AcOH), trifluoroacetic acid (TFA), methanesulfonic acid (MsOH), methanesulfonylchloride (MsCl), and *p*-toluenesulfonylchloride (TsCl) organic acids, 6-aminopyrazolo[3,4-*d*]pyrimidine

product **2a** and pyrazolo[3,4-*d*]pyrimidine product **3a**, were produced in 13–57% and 33–52% yields, respectively (Table 1, entries 4–8). Based on this result, the reactivity tendency of acid-mediated solvents was revealed to be in the order of methanesulfonylchloride (MsCl) > methanesulfonic acid (MsOH) > *p*-toluenesulfonylchloride (TsOH) > TFA > AcOH > aqueous acid solvents. In particular, the optimal result with a 57% yield with 6-aminopyrazolo[3,4-*d*]pyrimidine product **2a** was achieved by using methanesulfonylchloride (MsCl) as the acid-mediated solvent. In next attempt to optimization study, we used different amounts of cyanamide ($NH_2C{\equiv}N$) including 1.0, 2.0, 3.0, and 4.0 equivalents. The resulting 6-aminopyrazolo[3,4-*d*]pyrimidine **2a** was isolated in 19–57% yields, especially for 3.0 equivalent of $NH_2C{\equiv}N$ in the better yield (57%, Table 1, entries 8–11). Based on the above experimental result and cost consideration, the 3.0 equivalent of $NH_2C{\equiv}N$ is the most appropriate amount in the reaction condition.

Table 1. Optimization of Reaction Conditions for Synthesis of 6-Aminopyrazolo[3,4-*d*]pyrimidine



1a **2a** **3a**

Entry	Solvent	Equiv. of $NH_2C{\equiv}N$	Reaction condition	Yields (%)[b]	
				2a	**3a**
1	35% $HCl_{(aq)}$	3	at reflux (~101 °C)/3 h	-[a]	62
2	35% $HCl_{(aq)}$/AcOH (2 : 8)	3	at reflux (~105 °C)/3 h	-[a]	56
3	35% $HCl_{(aq)}$/AcOH (1 : 9)	3	at reflux (~107 °C)/3 h	-[a]	48
4	AcOH	3	at reflux (~113 °C)/3 h	13	-[a]
5	TFA	3	at reflux (~69 °C)/3 h	16	52

6	TsCl	3	at reflux (~131 °C)/3 h	33	-[a]
7	MsOH	3	~160 °C/3 h	37	47
8	MsCl	3	at reflux (~157 °C)/3 h	57	33
9	MsCl	4	at reflux (~157 °C)/3 h	48	39
10	MsCl	2	at reflux (~157 °C)/3 h	28	48
11	MsCl	1	at reflux (~157 °C)/3 h	19	33
12	MsCl	3	85–95 °C/6 h	52	27
13	MsCl	3	65–75 °C/8 h	57	12
14	MsCl	3	50–60 °C/10 h	63	8
15	MsCl	3	MW/65–75 °C/50 min	71	15
16	MsCl	3	MW/50–60 °C/2 h	83	6
17	MsCl/THF	3	MW/50–60 °C/2 h	44	39
18	MsCl/EtOH	3	MW/50–60 °C/2 h	-[a]	-[a]

[a]not-detectable.

[b]All of yields were obtained via chromatography purification.

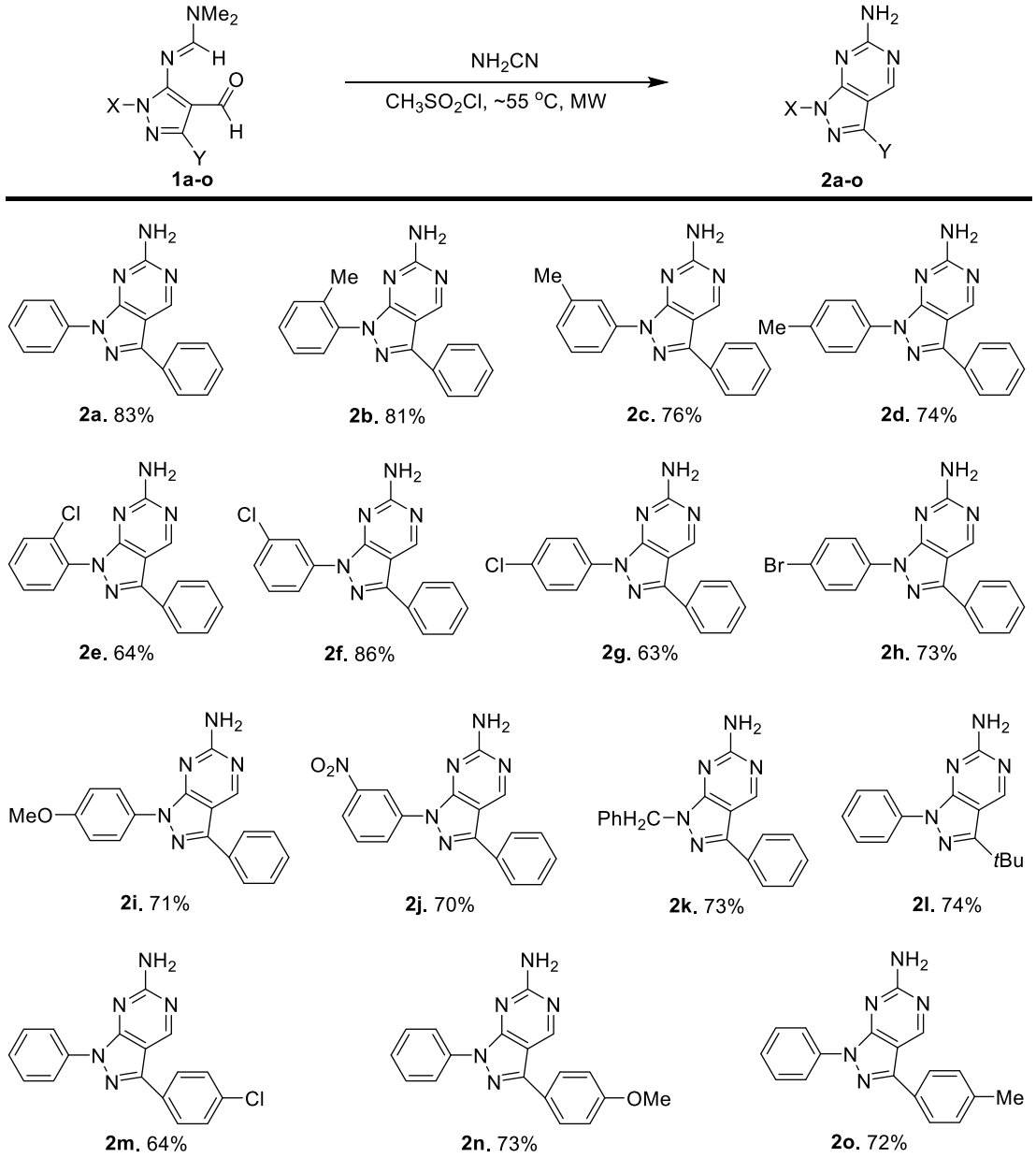
We then examined the effect of the reaction conditions on the ratio of **2a**/**3a**. Compound **2a** underwent a further deamination reaction to form compound **3a** under the above-mentioned reflux conditions. Consequently, we attempted to adjust the reaction time and temperature from reflux to ~50, 70, and 90°C, respectively (Table 1, entries 12–14). Reducing the reaction temperature and prolonging the reaction time impacted positively on the acid-promoted heterocyclization, with 6-aminopyrazolo[3,4-*d*]pyrimidine product **2a** yielding 52%, 57% and 63%, from progressively higher to lower ranges in temperature, respectively (Table 1, entries 12–14). However, a moderate amount of starting material **1a** was recovered under a mild reaction condition.

Microwave irradiation was utilized to facilitate this developed reaction owing to

it raises the temperature of the whole volume simultaneously (bulk heating) for increasing efficiency in many organic reactions to accelerate chemical transformation and increase higher yields in comparison with conventional heating.[37] Thus, we designed a heterocyclization reaction planned to synthesize 6-aminopyrazolo[3,4-d]pyrimidines by reacting 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** with 3.0 equivalent of cyanamide ($NH_2C{\equiv}N$) in a methanesulfonylchloride solution under microwave irradiation. The model procedure involved the treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidine **1a** with 3.0 equivalents of $NH_2C{\equiv}N$ in methanesulfonylchloride solution at ~55 °C or ~70 °C with 100W of microwave energy within 50 min or 2 h, respectively. When the aminating cyclization reaction was completed, the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidine product **2a** was obtained in 71% and 83% yields, respectively (Table 1, entries 15–16). These results demonstrated that the microwave-assisted synthetic technique efficiently optimizes the yield of 6-aminopyrazolo[3,4-*d*]pyrimidine product **2a** and positions pyrazolo[3,4-*d*]pyrimidine **3a** as the minor product. On the other hands, the co-solvent systems containing MsCl/THF or MsCl/EtOH (ratio = 1/1) were tried to perform under the same condition. However, they were unbeneficial for improvement of this reaction (Table 1, entries 17–18).

After applying the above standard procedure to 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1b**–**k** bearing various *N*-1 substituents, including *o*-, *m*-, *p*-Me-Ph, *o*-, *m*-, *p*-Cl-Ph, *p*-Br-Ph, *p*-OMe-Ph, *m*-NO_2-Ph, and $-CH_2Ph$, the aminating cyclization proved feasible to produce corresponding 6-aminopyrazolo[3,4-*d*]pyrimidines **2b**–**k** in 63–86% yields (Scheme 2). Furthermore, the substitution effect focused on the C-3 position of pyrazolic ring containing *t*-butyl,

p-Cl-Ph, *p*-OMe-Ph, and *p*-Me-Ph groups of compounds **1l**–**o**. The reactions successfully resulted in corresponding **2l**–**o** products in 64–74% yields (Scheme 2). In comparison with compound **1a**, we obtained lower isolated yields with grafting *t*-butyl (**1l**), *p*-Cl-Ph (**1m**), *p*-OMe-Ph (**1n**), and *p*-Me-Ph (**1o**) groups on the *C*-3 position of the pyrazolic ring. The simple and co-plane phenyl group favored the performance of the aminating cyclization reaction. All 6-aminopyrazolo[3,4-*d*]pyrimidines **2a**–**o** were fully characterized by spectroscopic methods. For example, compound **2a** presented one singlet peaks at δ 9.06 ppm of pyrimidinic ring in ^{1}H NMR. In FT-IR spectrum, compound **2a** exhibited characteristic broad absorption at 3454 cm^{-1}. The structure of compound **2c** was also characterized by X-ray crystallographic analysis (as the single-crystal X-ray diffraction study, ORTEP).

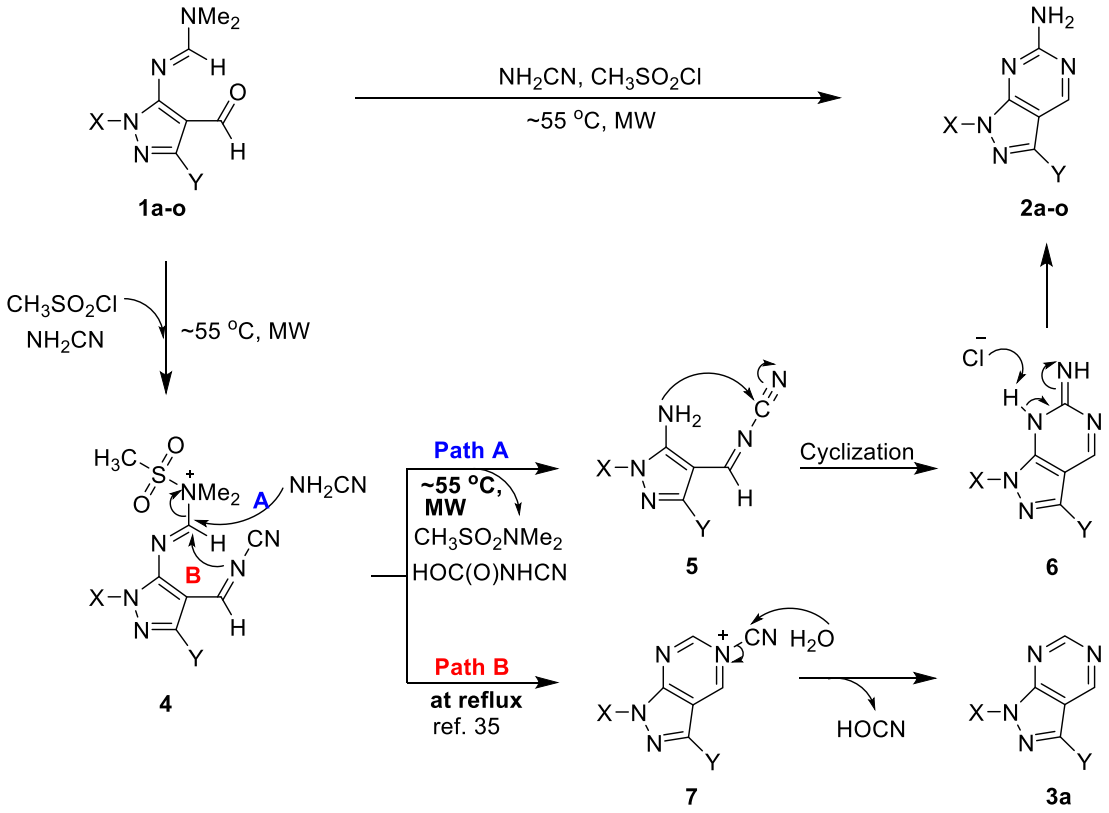


Scheme 2. Scope of Microwave-assisted Synthesis of 6-Aminopyrazolo[3,4-*d*]pyrimidines

Based on our control experimental studies, as well as previously reported results,[20,38] we predicted a plausible mechanism as shown in Scheme 3, to account for the formation of 6-aminopyrazolo[3,4-*d*]pyrimidines **2**. At first, amidines **1a**–**o** were used to simultaneously perform the imination and acid promoted reactions by cyanamide ($NH_2C{\equiv}N$) and methanesulfonylchloride to convert to the activated sulfonamide cation intermediate **4**.[38] Under microwave heating, deamination

effectively provided *N*-[(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]cyanamide intermediate **5** (**Path A**). Cyanamide ($NH_2C{\equiv}N$) was reacted towards intermediate **5** to produce an intramolecular cyclization to generate compound **6**. After the proton transformation, the final products 6-aminopyrazolo[3,4-*d*]pyrimidines **2a**–**o** were generated to accomplish acid-promoted heterocyclization and aromatization.

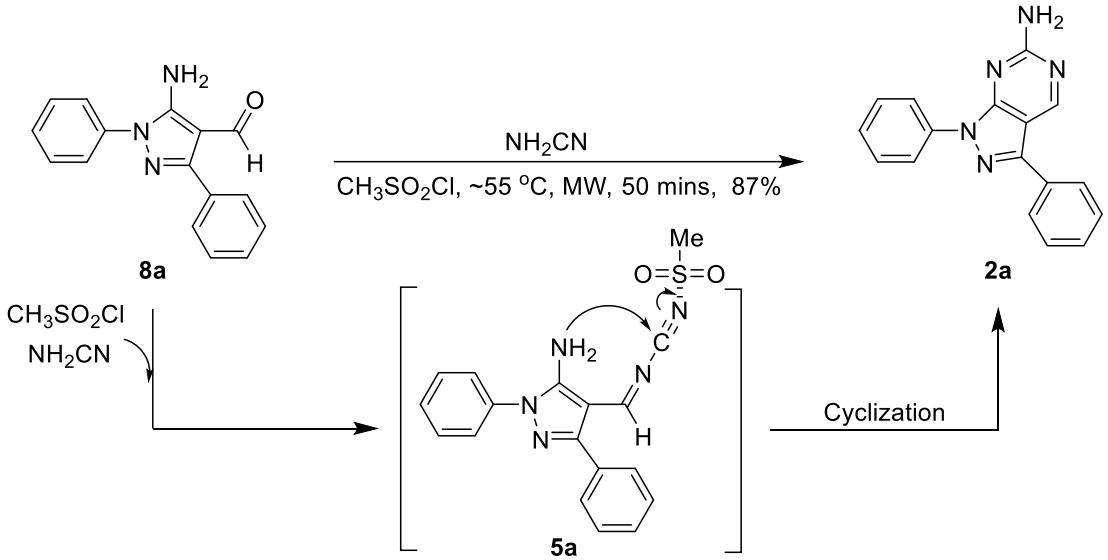
In **Path B**, the intramolecular cyclization of intermediate **4** was effectively realized under a high temperature heating reaction. Subsequently, the decyanation reaction took place by nucleophiles (e.g., water or excess cyanamide) to generate the pyrazolo[3,4-d]pyrimidine product **3a**. A similar result and mechanism has been predicted and demonstrated by the LC-MS analysis technique.[36]



Scheme 3. Proposed Reaction Mechanism

According to the predicted mechanism, 5-amino-1*H*-pyrazole-4-carbaldehyde

8a[38] was considered to be the deprotected form of compound **1a**. Theoretically, compound **8a** could be used to react with cyanamide ($NH_2C{\equiv}N$) in methanesulfonylchloride solution at ~55 °C with 100W of microwave energy within 50 min to give the same 6-aminopyrazolo[3,4-*d*]pyrimidines **2a**. Remarkably, we obtained this result and isolated the product **2a** in 87% yield (Scheme 4). On the other hand, intermediate **5a** was expected as the chemical synthetic equivalent of intermediate **5** (Schemes 3 and 4). Fortunately, intermediate **5** was also successfully isolated and fully characterized by spectroscopic methods. For example, *N*-[(5-amino-1,3-diphenyl-1*H*-pyrazol-4-yl)methylene]cyanamide **5** presented a singlet peak at δ 8.86 ppm for –CH=N–C≡N in ^{1}H NMR (Figure 1) and exhibited two characteristic peaks at 118.10 ppm for N–C≡N and 171.74 ppm for –*C*H=N–C≡N, which represented the ^{13}C in NMR. The IR absorptions of **5** showed peaks at 2184 cm^{-1} for stretching of the –C≡N group and at 3288 and 3391 cm^{-1} for stretching of the $–NH_2$ group.



Scheme 4. **Demonstration Study of Mechanism**

In further investigations, the timed programming of the acid promoted heterocyclization reaction was conducted under microwave irradiation to demonstrate

the mechanism and is shown in Figure 1. The reaction mixture was sampled every 20 min and analyzed by the ^{1}H-NMR spectroscopic method. This result led us to consider that starting material **8a** was gradually converted to the imination intermediate **5a**. Subsequently, the acid-promoted heterocyclization reaction occured and most of the starting material **8a** and intermediate **5a** was successfully transferred to the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidines product **2a** in 87% yield. Therefore, we speculated that the starting material **8a** diminished and progressively transformed into the intermediate compound **5a**, which subsequently cyclized into **2a** under the acidic condition (Scheme 4 and Figure 1). The experimental results support our proposed mechanism.

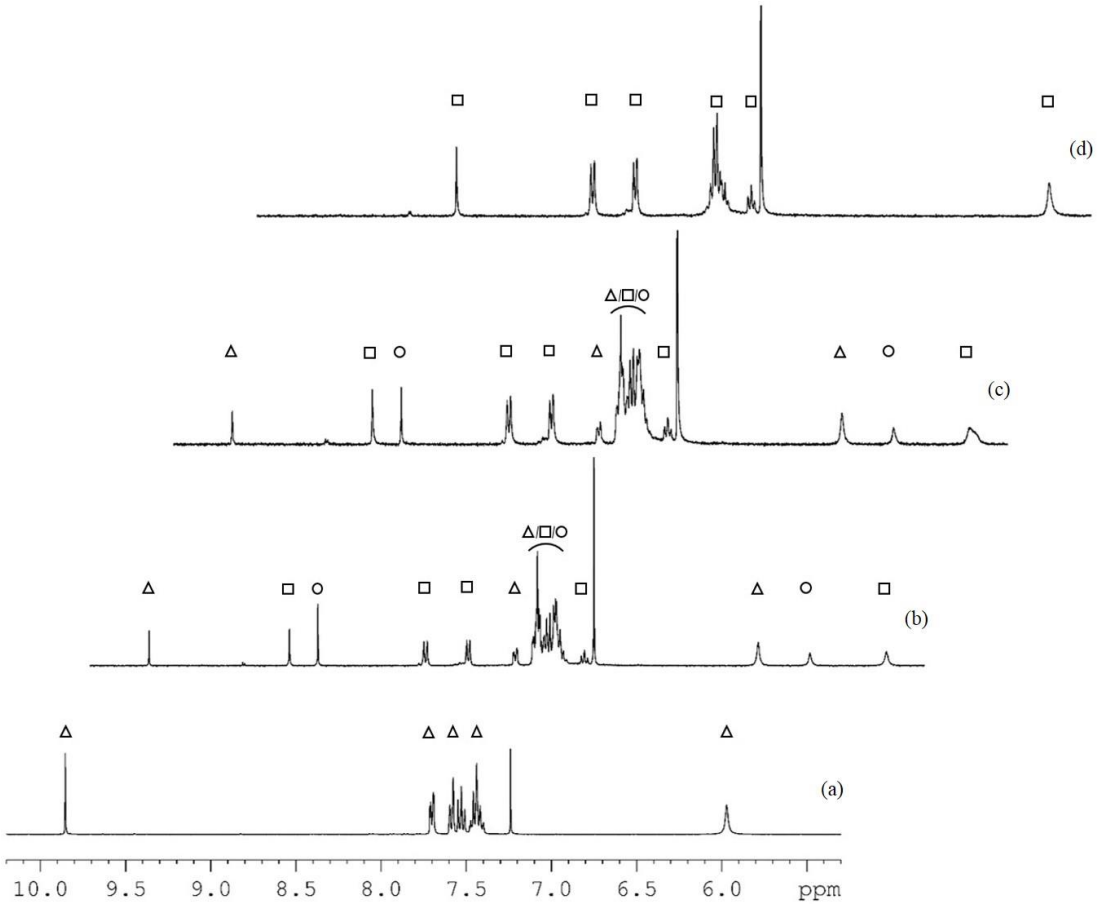
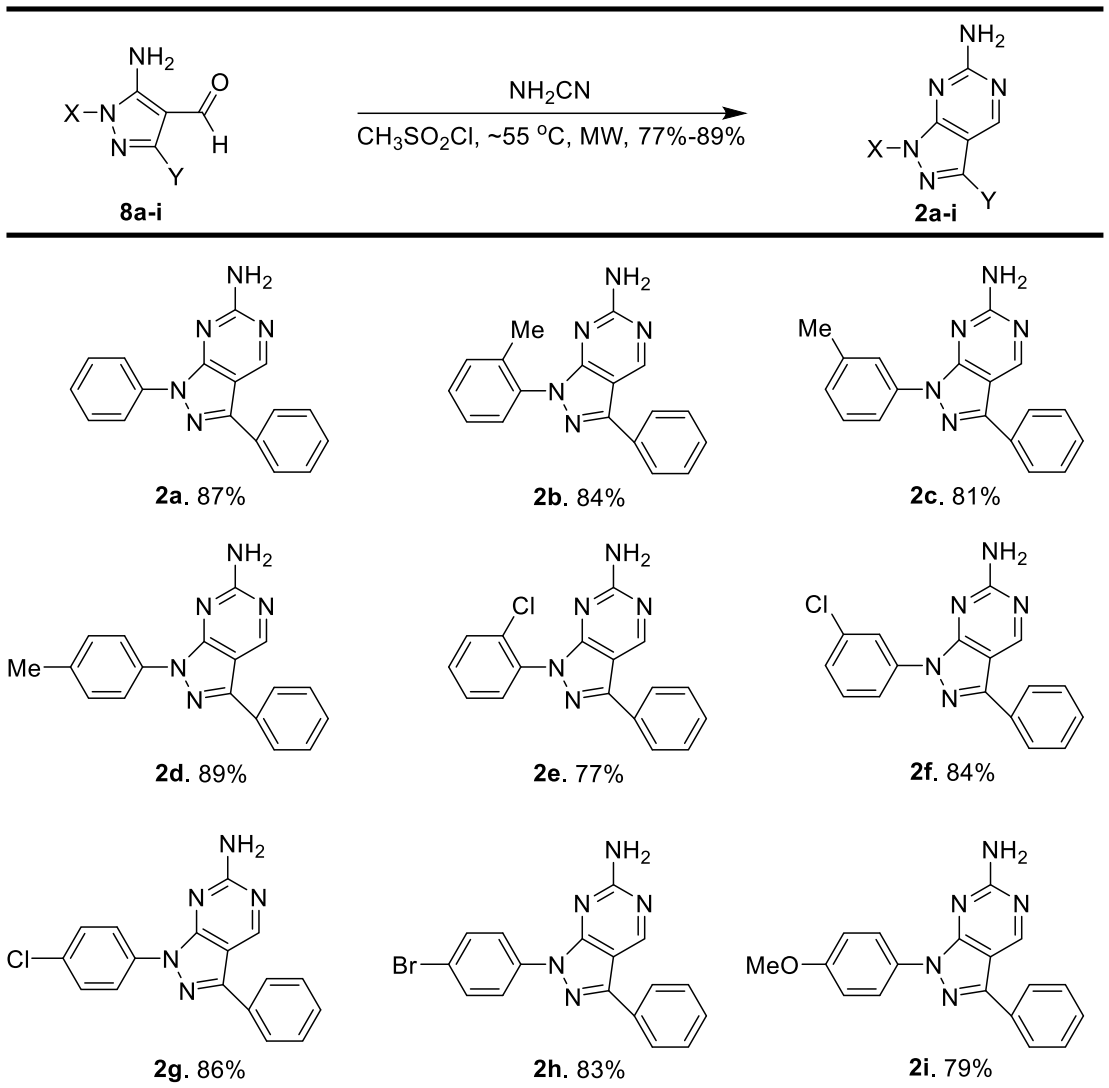


Figure 1. (a) The reaction condition was started at ~55 °C (Δ: ^{1}H NMR of the starting material **8a**). (b, c) Reaction conditions at ~55 °C for 20 and 40 min (^{1}H NMR of ○: intermediate **5a**). (d) The reaction condition at ~55°C for 50 min (□: ^{1}H NMR of

6-aminopyrazolo[3,4-*d*]pyrimidines product **2a**).

To continue our exploratory study, a series of 5-amino-1*H*-pyrazole-4-carbaldehydes **8a**–**i** were prepared[39,40] and probed as model substrates for acid-promoted heterocyclization under microwave irradiation. This procedure was applied to 5-amino-1*H*-pyrazole-4-carbaldehydes **8b**–**i** bearing various substituents, including *o*-, *m*-, *p*-Me, *o*-, *m*-, *p*-Cl, *p*-Br, and *p*-OMe, and the one-pot acid-promoted heterocyclization smoothly underwentat 50–60 °C with 100W of microwave energy within 50 min to generate the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidine products **2b**–**i** in good yields (77–89%, Scheme 5). All 6-aminopyrazolo[3,4-*d*]pyrimidines **2a**–**i** were confirmed and fully characterized using the ^{1}H-NMR spectroscopic method. In comparison with 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1** and 5-amino-1*H*-pyrazole-4-carbaldehydes **8** as the starting reactants, we found that compounds **8** can provide higher isolated yields (77–89% yields, Scheme 5). Based on the manufacturing steps and commercial costs, we believed that 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1** were easily prepared and adaptable for generating the desired 6-aminopyrazolo[3,4-*d*]pyrimidines **2**.



Scheme 5. Scope of Microwave-assisted Synthesis Methdology

CONCLUSIONS

We have developed a microwave-assisted acid-promoted synthesis of 6-aminopyrazolo[3,4-*d*]pyrimidines by treating 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines or 5-amino-1*H*-pyrazole-4-carbaldehydes with cyanamide ($NH_2C{\equiv}N$) under an acid-mediated solution. A scanning optimization study determined that methanesulfonylchloride was the most appropriate solvent to use in an acid-mediated solution. Microwave irradiation produced a superior reaction condition compared with the conventional heating condition. According to our results, greater isolated yields of

6-aminopyrazolo[3,4-*d*]pyrimidines are synthesized from 5-amino-1*H*-pyrazole-4-carbaldehydes **8** than from 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1**. In consideration of the route of synthesis and commercial costs, 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines **1** were favored as the starting materials to prepare 6-aminopyrazolo[3,4-*d*]pyrimidines.

EXPERIMENTAL SECTION

General Procedure: Starting substrates **1a**–**o**[39] and **8a**–**h**[40] are synthesized according to our previously reported methods. 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines, **1a**,[39,40] **1c**,[40] **1d**,[41] **1e**–**f**,[40] **1g**,[41] **1h**–**j**,[40] and **1l**–**o**,[40] and 5-amino-1*H*-pyrazole-4-carbaldehyde **8a**[39] are all known compounds, and their physical and spectral data were consistent with those previously reported. Other reagents were commercially available and were used directly without further purification. Analytical thin-layer chromatography was performed on 0.25 mm silica gel 60-F254. Visualization was carried out with UV light. ^{1}H NMR was recorded on a Bruker instrument (400 or 500 MHz). Chemical shifts were quoted in parts per million (ppm) referenced to 0.0 ppm for tetramethylsilane and referenced to residual protium in the NMR solvent ($CDCl_3$ = δ 7.24). The following abbreviations (or combinations thereof) were used to explain multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Coupling constants, J, were reported in hertz (Hz). ^{13}C NMR spectra were recorded on a Bruker instrument (100 or 125 MHz) and were fully decoupled by broad band proton decoupling. Chemical shifts were reported in ppm and referenced to the center line of a triplet at 77.0 ppm of chloroform-*d*. Infrared (IR) spectra were recorded as neat solutions or solids; mass spectra were recorded using electron impact or electrospray ionization techniques. The wavenumbers reported are referenced to the polystyrene 1601 cm^{-1} absorption.

High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-HX110 mass spectrometer with an electron ionization (EI) source.

Microwave Irradiation Experiments. All microwave irradiation experiments described herein were performed with a single-mode Discover Labmate System from CEM Corporation, using a 25 mL Pyrex round-bottomed flask for open-vessel heating chemical reactions. Experiments were performed under a controlled temperature mode, subjecting the open vessel to temperatures of between 50 °C and 75 °C for 50 min or 2 h. In all experiments, the internal reaction temperature was monitored by an FO probe sensor. Conventional heating was performed with a standard hot plate/magnetic stirrer for comparison experiments.

Standard Procedure for the Synthesis of 1*H*-Pyrazol-5-yl-*N*,*N*-dimethylformamidines (1a–o).[39,40] A solution of pyrazol-5-amine derivatives (4.00 mmol, 1.0 equiv) and $POCl_3$ (4.80 mmol, 1.2 equiv) in DMF solution (12 mL) at 30–40 °C was treated with 100 W of microwave energy within 10–20 min. When the reaction was completed, the reaction mixture was concentrated, added to water (10 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel using hexane/ethyl acetate as eluent to give the corresponding 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines products (**1a**–**o**) in 81–96% yields.

*N'-(4-Formyl-1,3-diphenyl-1H-pyrazol-5-yl)-N,N-dimethyl-methanimidamide (**1a**)* It was obtained in 93% yield as a yellow solid (1.18 g); mp 126–127 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (s, 3H), 3.14 (s, 3H), 7.26–7.30 (m, 1H), 7.39–7.47 (m, 5H), 7.68 (dd, *J* = 9.90, 1.49 Hz, 2H), 7.68 (dd, *J* = 12.5, 1.09 Hz, 2H), 8.71 (s, 1H), 9.69 (s, 1H).[39,40]

*N'-[4-Formyl-1-(2-methylphenyl)-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1b**)* A solution of 1-(2-methylphenyl)-3-phenyl-1*H*-pyrazol-5-amine (1.00 g, 4.0 mmol) and $POCl_3$ (0.44 mL, 4.8 mmol) in DMF solution (12 mL) at 30–40 °C was treated with 100 W of microwave energy within 10–20 min. When the reaction was completed, the reaction mixture was concentrated, added to water (10 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel (hexane/EtOAc = 7:3) to give pure **1b**; 83% yields (1.10 g), yellow solid; mp 102–105 °C.^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.20 (s, 3H), 2.81 (s, 3H), 3.07 (s, 3H), 7.22–7.29 (m, 3H), 7.32 (d, *J* = 7.45 Hz, 1H), 7.39–7.45 (m, 3H), 7.68 (dd, *J* = 8.10, 1.37 Hz, 2H), 8.83 (s, 1H), 9.73 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 18.22, 34.0, 40.6, 107.5 126.1, 128.0, 128.4 (2 × C), 128.65, 128.69, 129.4 (2 × C), 130.5, 132.5, 135.7, 138.1, 154.7, 155.8, 158.8, 185.2. IR (KBr): 2922, 1662, 1625, 1478, 1389, 1114, 1092 cm^{-1}. EIMS m/z: 333 (24), 332 (M^+, 100), 331 (10), 317 (41), 289 (16), 288 (43), 277 (15), 260 (20), 90 (11). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{20}N_4O$: 332.1637; Found 332.1636.

*N'-[4-Formyl-1-(3-methylphenyl)-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1c**)* It was obtained in 84% yield as a brown solid (1.12 g); mp 119–121 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.38 (s, 3H), 3.03 (s, 3H), 3.14 (s, 3H), 7.10 (d, *J* = 7.50 Hz, 1H), 7.29 (d, *J* = 7.79 Hz, 1H), 7.41–7.46 (m, 3H), 7.66–7.67 (m, 4H), 8.70 (s, 1H), 9.69 (s, 1H).[40]

*N'-[4-Formyl-1-(4-methylphenyl)-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1d**)* It was obtained in 96% yield as a light yellow solid (1.28 g); mp 154–156 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.37 (s, 3H), 3.02 (s, 3H), 3.14 (s, 3H), 7.21 (d, *J* = 8.33 Hz, 2H), 7.40–7.46 (m, 3H), 7.67 (d, *J* = 7.29 Hz, 2H), 7.73 (d, *J* =

8.31 Hz, 2H), 8.70 (s, 1H), 9.68 (s, 1H).[41]

*N'-[1-(2-Chlorophenyl)-4-formyl-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1e**)*: It was obtained in 81% yield as a brown solid (1.14 g); mp 134–135 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.83 (s, 3H), 3.01 (s, 3H), 7.30–7.36 (m, 2H), 7.40–7.45 (m, 3H), 7.47–7.49 (m, 2H), 7.68 (d, *J* = 7.94 Hz, 2H), 8.93 (s, 1H), 9.73 (s, 1H).[40]

*N'-[1-(3-Chlorophenyl)-4-formyl-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1f**)*: It was obtained in 88% yield as a light yellow solid (1.24 g); mp 145–146 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.07 (s, 3H), 3.17 (s, 3H), 7.24–7.26 (m, 1H), 7.34 (t, *J* = 8.08 Hz, 1H), 7.42–7.47 (m, 3H), 7.66 (dd, *J* = 7.85, 1.31 Hz, 2H), 7.84 (dd, *J* = 8.25, 0.79 Hz, 1H), 8.05 (t, *J* = 1.90 Hz, 1H), 8.77 (s, 1H), 9.68 (s, 1H).[40]

*N'-[1-(4-Chlorophenyl)-4-formyl-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1g**)*: It was obtained in 86% yield as a light yellow (1.21 g); mp 159–161 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.04 (s, 3H), 3.16 (s, 3H), 7.38 (dd, *J* = 6.83, 2.03 Hz, 2H), 7.42–7.47 (m, 3H), 7.66 (dd, *J* = 7.95, 1.49 Hz, 2H), 7.86 (dd, *J* = 6.84, 2.01 Hz, 2H), 8.75 (s, 1H), 9.68 (s, 1H).[41]

*N'-[1-(4-Bromophenyl)-4-formyl-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1h**)*: It was obtained in 86% yield as a yellow (1.37 g); mp 171–173 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.04 (s, 3H), 3.16 (s, 3H), 7.42–7.47 (m, 3H), 7.53 (dd, *J* = 6.90, 1.94 Hz, 2H), 7.65 (dd, *J* = 7.95, 1.40 Hz, 2H), 7.81 (dd, *J* = 6.94, 1.89 Hz, 2H), 8.75 (s, 1H), 9.67 (s, 1H).[40]

*N'-[4-Formyl-1-(4-methoxyphenyl)-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1i**)*: It was obtained in 93% yield as a light yellow (1.30 g); mp 146–149 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.01 (s, 3H), 3.14 (s, 3H), 3.82 (s, 3H), 6.93 (dd, *J* = 6.89, 1.87 Hz, 2H), 7.40–7.46 (m, 3H), 7.67 (dd, *J* = 8.10, 1.44 Hz, 2H), 7.74 (dd,

J = 6.88, 2.18 Hz, 2H), 8.72 (s, 1H), 9.68 (s, 1H).[40]

*N'-[4-Formyl-1-(3-nitrophenyl)-3-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimid amide (**1j**)*: It was obtained in 84% yield as a yellow (1.22 g); mp 218–220 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.13 (s, 3H), 3.21 (s, 3H), 7.45–7.49 (m, 3H), 7.58 (t, *J* = 8.21 Hz, 1H), 7.68 (dd, *J* = 7.85, 1.48 Hz, 2H), 8.11 (dd, *J* = 8.22, 1.40 Hz, 1H), 8.36 (dd, *J* = 8.16, 1.11 Hz, 1H), 8.90 (s, 1H), 9.19 (t, *J* = 2.10 Hz, 1H), 9.68 (s, 1H).[40]

*N'-(1-Benzyl-4-formyl-3-phenyl-1H-pyrazol-5-yl)-N,N-dimethyl-methanimidamide (**1k**)* A solution of 1-benzyl-3-phenyl-1*H*-pyrazol-5-amine (1.00 g, 4.0 mmol) and $POCl_3$ (0.44 mL, 4.8 mmol) in DMF solution (12 mL) at 30–40 °C was treated with 100 W of microwave energy within 10–20 min. When the reaction was completed, the reaction mixture was concentrated, added to water (10 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel (hexane/EtOAc = 8:2) to give pure **1k**; 89% yields (1.18 g), yellow solid; mp 101–102 °C.^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.07 (s, 3H), 3.13 (s, 3H), 5.34 (s, 2H), 7.22–7.24 (m, 1H), 7.27–7.33 (m, 4H), 7.37–7.43 (m, 3H), 7.58 (d, *J* = 6.78 Hz, 2H), 8.99 (s, 1H), 9.62 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 34.1, 40.7, 51.0, 107.7, 127.4, 127.9 (2 × C), 128.38 (2 × C),128.41 (2 × C), 128.50, 129.4 (2 × C), 132.6, 137.2, 153.4, 155.4, 160.0, 185.9. IR (KBr): 2924, 1662, 1622, 1479, 1383, 1113, 701 cm^{-1}. EIMS m/z: 333 (12), 332 (M^+, 57), 255 (20), 245 (13), 91 (100), 83 (79). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{20}H_{20}N_4O$: 332.1637; Found 332.1632.

*N'-[4-Formyl-3-t-butyl-1-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1l**)* : It was obtained in 83% yield as a brown (0.99 g); mp 117–120 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.44 (s, 9H), 3.02 (s, 3H), 3.07 (s, 3H), 7.21–7.24 (m, 1H), 7.37 (t, *J* = 7.91 Hz, 2H), 7.81 (d, *J* = 7.59, 2H), 7.96 (s, 1H), 9.77 (s, 1H).[40]

*N'-[3-(4-Chlorophenyl)-4-formyl-1-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1m**)* : It was obtained in 92% yield as a brown (1.30 g); mp 133–135 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.03 (s, 3H), 3.14 (s, 3H), 7.29 (t, *J* = 7.43 Hz, 1H), 7.40–7.43 (m, 4H), 7.65 (d, *J* = 8.49, 2H), 7.84 (d, *J* = 7.58, 2H), 8.62 (s, 1H), 9.65 (s, 1H).[40]

*N'-[4-Formyl-3-(4-methoxylphenyl)-1-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1n**)* : It was obtained in 94% yield as a light yellow (1.31 g); mp 136–138 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.02 (s, 3H), 3.14 (s, 3H), 3.84 (s, 3H), 6.98 (d, *J* = 8.68, 2H), 7.27 (t, *J* = 7.42, 1H), 7.41 (t, *J* = 7.89, 2H), 7.62 (d, *J* = 2.89, 2H), 7.86 (d, *J* = 8.18, 2H), 8.67 (s, 1H), 9.67 (s, 1H).[40]

*N'-[4-formyl-3-(4-methylphenyl)-1-phenyl-1H-pyrazol-5-yl]-N,N-dimethyl-methanimidamide (**1o**)* : It was obtained in 96% yield as a brown (1.28 g); mp 124–125 ℃; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.39 (s, 3H), 3.03 (s, 3H), 3.14 (s, 3H), 7.24–7.29 (m, 3H), 7.41 (t, *J* = 7.91 Hz, 2H), 7.57 (d, *J* = 7.85, 2H), 7.86 (d, *J* = 7.77, 2H), 8.70 (s, 1H), 9.68 (s, 1H).[40]

Method A: Standard Procedure of Scanning Acid-mediated Solvents for Synthesis of 6-Aminopyrazolo[3,4-*d*]pyrimidine 2a and pyrazolo[3,4-*d*]pyrimidine 3a. The procedure involved the treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines (**1a**, 1.0 equiv) with 3.0 equivalent of cyanamide ($NH_2C{\equiv}N$) in aqueous conc. HCl, $HCl_{(aq)}$/AcOH co-solvent, acetic acid (AcOH), trifluoroacetic acid (TFA), methanesulfonic acid, methanesulfonylchloride/THF, methanesulfonylchloride/EtOH co-solvent, methanesulfonylchloride, or *p*-toluenesulfonylchloride solution (2.0 mL) at reflux, 50–60 °C, 65–75 °C, or 85–95 °C, for 3, 6, 8, or 10 h. When the reaction was completed (monitored by TLC), the resulting mixture was added to water (15 mL) and

extracted with dichloromethane (2 × 15 mL). The organic extracts were washed with saturated sodium bicarbonate (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel using CH_2Cl_2/ethyl acetate as eluent to give the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidine **2a** or/and pyrazolo[3,4-*d*]pyrimidine **3a** product.

*6-Amino-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**2a**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.38(br, 2H), 7.29 (t, *J* = 7.38 Hz, 1H), 7.43–7.53(m, 5H), 7.98 (d, *J* = 7.16 Hz, 2H), 8.23 (d, *J* = 7.80 Hz, 2H), 9.06 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 108.6, 121.2 (2 × C), 126.2, 127.3 (2 × C), 129.0 (2 × C), 129.1 (2 × C), 129.3, 132.0, 138.9, 145.5, 154.3, 155.9, 161.5.

*1,3-Diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**3a**).* ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (t, *J* = 7.42 Hz, 1H), 7.45–7.49 (m, 1H), 7.54 (t, *J* = 15.49 Hz, 4H), 8.04 (d, *J* = 7.11 Hz, 2H), 8.29 (d, *J* = 7.63 Hz, 2H), 9.11 (s, 1H), 9.48 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 114.2, 121.4 (2 × C), 126.8, 127.3 (2 × C), 129.2 (4 × C), 129.6, 131.4, 138.5, 144.9, 152.8, 153.3, 155.5. Physical and spectral data were consistent with those previously reported.[42]

Method B: Standard Procedure for Synthesis of 6-Aminopyrazolo[3,4-*d*]pyrimidines (2a–o). The reliable procedure involved the treatment of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines (**1a**–**o**, 1.0 equiv) with 3.0 equivalent of cyanamide ($NH_2C{\equiv}N$) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel using CH_2Cl_2/ethyl acetate as the

eluent to give the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidine products (**2a**–**n**) in 63–86% yields.

*6-Amino-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**2a**).* The standard procedure involved the treatment of *N*′-(4-formyl-1,3-diphenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-methanimidamide (**1a**, 98.7 mg, 0.31 mmol, 1.0 equiv) with cyanamide (39.1 mg, 0.93 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2a**; 83% yields (73.9 mg), yellow solid; mp 167–168 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (br, 2H), 7.29 (t, *J* = 7.40 Hz, 1H), 7.45–7.54 (m, 5H), 7.98 (d, *J* = 7.24 Hz, 2H), 8.24 (d, *J* = 7.88 Hz, 2H), 9.06 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 108.6, 121.2 (2 × C), 126.1, 127.2 (2 × C), 129.01 (2 × C), 129.03 (2 × C), 129.3, 132.0, 138.9, 145.5, 154.3, 155.9, 161.4. IR (KBr): 3474, 3416, 2058, 1643, 1632, 1557 cm^{-1}. EIMS m/z: 288 (20), 287 (M^+, 100), 286 (50), 272 (33), 271 (13), 77 (26). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{13}N_5$: 287.1171; Found 287.1163.

*6-Amino-1-(2-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2b**).* The standard procedure involved the treatment of *N*′-[4-formyl-1-(2-methylphenyl)-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methani midamide (**1b**, 103 mg, 0.31 mmol, 1.0 equiv) with cyanamide (39.1 mg, 0.93 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h.When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with

dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2b**; 81% yields (75.7 mg), white solid; mp 207–208 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (s, 3H), 5.43 (br, 2H), 7.33–7.40 (m, 3H), 7.42–7.46 (m, 2H), 7.50 (t, *J* = 7.36 Hz, 2H), 7.96 (d, *J* = 7.08 Hz, 2H), 9.08 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 18.3, 107.2, 126.7, 127.2 (2 × C), 127.8, 129.1 (2 × C), 129.2, 129.3, 131.3, 132.0, 135.8, 136.3, 145.6, 153.6, 156.5, 161.2. IR (KBr): 3416, 3400, 2039, 2014, 1694, 1614, 1597, 1557, 1514, 1470, 1410, 1275, 1165 cm^{-1}. EIMS m/z: 302 (19), 301 (M^+, 100), 300 (42), 224 (6), 221 (9). 147 (6). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{15}N_5$: 301.1327; Found 301.1331.

*6-Amino-1-(3-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2c**).* The standard procedure involved the treatment of *N*'-[4-formyl-1-(3-methylphenyl)-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1c**, 96.4 mg, 0.29 mmol, 1.0 equiv) with cyanamide (36.6 mg, 0.87 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2c**; 76% yields (66.4 mg), white solid; mp 161–162 °C (hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.44 (s, 3H), 5.45 (br, 2H), 7.11 (d, *J* = 7.48 Hz, 1H), 7.37 (t, *J* = 7.83 Hz, 1H), 7.44 (t, *J* = 7.32 Hz, 1H), 7.51 (t, *J* = 7.42 Hz, 2H), 7.97 (d, *J* = 0.48 Hz, 1H), 7.98 (s, 2H), 8.01 (d , *J* = 8.12 Hz, 1H), 9.04 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.6, 108.5, 118.6, 121.9, 127.1, 127.2 (2 × C), 128.8, 129.0 (2 × C), 129.2,

132.1, 138.7, 139.0, 145.4, 154.2, 155.8, 161.5. IR (KBr): 3439, 3418, 2070, 2064, 1651, 1643, 1634 cm^{-1}. EIMS m/z: 302 (22), 301 (M^+, 100), 300 (38). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{15}N_5$: 301.1327; Found 301.1321.

6-Amino-1-(4-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2d)****.* The standard procedure involved the treatment of *N*'-[4-formyl-1-(4-methylphenyl)-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1d**, 99.7 mg, 0.30 mmol, 1.0 equiv) with cyanamide (37.8 mg, 0.90 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2d**; 74% yields (66.9mg), white solid; mp 125–126 °C (Hexane–EtOAc). ^1H NMR ($CDCl_3$, 400 MHz): δ 2.39 (s, 3H), 5.33 (br, 2H), 7.29 (d, *J* = 8.40 Hz, 2H), 7.44–7.46 (m, 1H), 7.51 (dd, *J* = 14.80, 7.60 Hz, 2H), 7.98 (d, *J* = 7.60, 2H), 8.06 (d, *J* = 8.40, 2H), 9.04 (s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 21.1, 108.5, 121.3 (2 × C), 127.2 (2 × C), 129.0 (2 × C), 129.2, 129.5 (2 × C), 133.1, 136.0, 136.4, 145.2, 154.2, 155.7, 161.4. IR (KBr): 3439, 3424, 2197, 2154, 1636, 1559 cm^{-1}. EIMS m/z: 302 (22), 301 (M^+, 97), 300 (35), 224 (33). 198 (90), 197 (100). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{18}H_{15}N_5$: 301.1327; Found 301.1333.

6-Amino-1-(2-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2e)****.* The standard procedure involved the treatment of *N*'-[1-(2-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1e**, 116 mg, 0.33 mmol, 1.0 equiv) with cyanamide (41.6 mg, 0.99 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of

microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2e**; 64% yields (68.0 mg), brown solid; mp 61–62 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.48–7.51 (m, 3H), 7.55 (t, *J* = 7.40 Hz, 2H), 7.60–7.65 (m, 2H), 8.05 (d, *J* = 7.56 Hz, 2H), 9.08 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 113.1, 127.4 (2 × C), 127.7, 128.4, 129.3 (2 × C), 129.68, 129.71, 130.8, 131.4, 132.2, 134.8, 145.8, 152.9, 154.6, 155.9. IR (KBr): 3439, 3418, 2089, 1643, 1634, 1520, 1497, 1373, 1049 cm^{-1}. EIMS m/z: 321 (M^+, 12), 308 (35), 307 (21), 306 (100), 297 (15), 272 (19), 271 (92), 195 (13), 168 (10), 77 (26). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{12}ClN_5$: 321.0781; Found 321.0788.

6-Amino-1-(3-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2f)****.* The standard procedure involved the treatment of *N*'-[1-(3-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1f**, 123 mg, 0.33 mmol, 1.0 equiv) with cyanamide (44 mg, 1.05 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 8:2) to give pure **2f**; 86% yields (96.8 mg), light-yellow solid; mp 204–205 °C (hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (br, 2H), 7.23–7.26 (m, 1H), 7.41 (t, *J* = 8.13 Hz, 1H), 7.44–7.48 (m, 1H), 7.50–7.54 (m, 2H), 7.97 (dt, *J* = 6.48, 1.52 Hz, 2H), 8.24 (dq, *J* = 8.24, 0.98 Hz,

1H), 8.37 (t, *J* = 2.02 Hz, 1H), 9.04 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 108.8, 118.7, 120.8, 125.9, 127.29 (2 × C), 129.1 (2 × C), 129.5, 130.0, 131.8, 134.7, 140.0, 145.9, 154.4, 156.2, 161.5. IR (KBr): 3455, 3441, 3416, 2066, 1643, 1634, 1506 cm^{-1}. EIMS m/z: 323 (M^+ + 2, 34), 321 (M^+, 100), 322 (31), 320 (34). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{12}ClN_5$: 321.0781; Found 321.0784.

6-Amino-1-(4-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2g)****.* The standard procedure involved the treatment of *N'*-[1-(4-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanim idamide (**1g**, 113 mg, 0.32 mmol, 1.0 equiv) with cyanamide (40.4 mg, 0.96 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 2:8) to give pure **2g**; 63% yields (64.8 mg), light-yellow solid; mp 169–170 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (br, 2H), 7.46 (t, *J* = 7.48 Hz, 3H), 7.52 (t, *J* = 7.40 Hz, 2H), 7.96 (d, *J* = 7.20 Hz, 2H), 8.25 (d, *J* = 8.84 Hz, 2H), 9.04 (s, 1H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$): δ 108.7, 122.0 (2 × C), 127.2 (2 × C), 129.1 (4 × C), 129.4, 131.3, 131.8, 137.5, 145.8, 154.3, 155.9, 161.4. IR (KBr): 3287, 3154, 3113, 2916, 2849, 1634, 1591, 1489, 1402, 1192 cm^{-1}. EIMS m/z: 323 (M^+ + 2, 35), 322 (35), 321 (M^+, 100), 320 (40), 135 (16), 128 (11), 121 (11), 119 (10), 111 (86), 95 (20), 83 (14), 77 (26), 71 (16), 69 (27), 57 (32), 55 (14). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{12}ClN_5$: 321.0781; Found 321.0777.

6-Amino-1-(4-bromophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2h)****.* The standard procedure involved the treatment of

N'-[1-(4-bromophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1h**, 107 mg, 0.27 mmol, 1.0 equiv) with cyanamide (34.1 mg, 0.81 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 8:2) to give pure **2h**; 73% yields (72.2 mg), light-yellow solid; mp 161–162 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.32 (br, 2H), 7.47 (d, *J* = 7.22 Hz, 1H), 7.52 (t, *J* = 7.29 Hz, 2H), 7.60 (d, *J* = 8.83 Hz, 2H), 7.97 (d, *J* = 6.93 Hz, 2H), 8.20 (dd, *J* = 6.97, 1.93 Hz, 2H), 9.05 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 108.7, 119.1, 122.3 (2 × C), 127.2 (2 × C), 129.1 (2 × C), 129.4, 131.8, 132.0 (2 × C), 138.0, 145.8, 154.4, 156.0, 161.4. IR (KBr): 3285, 3156, 3107, 2957, 2926, 2855, 1634, 1586, 1487, 1398, 1273, 1123, 1072 cm^{-1}. EIMS m/z: 368 (21), 367 (M^+ + 2, 100), 366 (42), 365 (M^+, 99), 364 (22), 149 (11), 77 (13). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{12}BrN_5$: 365.0276; Found 365.0280.

*6-Amino-1-(4-methoxylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine **(2i)**.* The standard procedure involved the treatment of *N'*-[4-formyl-1-(4-methoxylphenyl)-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1i**, 132 mg, 0.38 mmol, 1.0 equiv) with cyanamide (47.9 mg, 1.14 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure and the residue was purified by

chromatography on silica gel (CH_2Cl_2/EtOAc = 17:3) to give pure **2i**; 71% yields (85.6 mg), light-yellow solid; mp 206–207 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 5.29 (br, 2H), 7.02 (dd, *J* = 6.98, 2.11 Hz, 2H), 7.45 (d, *J* = 7.61 Hz, 1H), 7.51 (t, *J* = 7.45 Hz, 2H), 7.97 (d, *J* = 7.10 Hz, 2H), 8.05 (dd, *J* = 6.92, 2.18 Hz, 2H), 9.04 (s, 1H). ^{13}C{^{1}H} NMR (100MHz, $CDCl_3$): δ 55.5, 108.3, 114.2 (2 × C), 123.1 (2 × C), 127.2 (2 × C), 129.0 (2 × C), 129.1, 132.0, 132.1, 145.1, 154.2, 155.4, 158.0, 161.4. IR (KBr): 3439, 3424, 2255, 1634, 1520, 1470, 1410 cm^{-1}. EIMS m/z: 318 (22), 317 (M^+, 100), 316 (15), 302 (15). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{15}N_5O$: 317.1277; Found 317.1273.

*6-Amino-1-(3-nitrophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2j**).* The standard procedure involved the treatment of *N′*-[4-formyl-1-(3-nitrophenyl)-3-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimi damide (**1j**, 98.1 mg, 0.27 mmol, 1.0 equiv) with cyanamide (34.1 mg, 0.87 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2j**; 70% yields (62.8 mg), yellow solid; mp 134–135 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.41 (br, 2H), 7.49–7.56 (m, 3H), 7.64–7.68 (m, 1H), 7.99 (d, *J* = 8.00 Hz, 2H), 8.11 (d, *J* = 8.00 Hz, 1H), 8.73 (d, *J* = 8.00 Hz, 1H), 9.08 (s, 1H), 9.33 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 108.9, 115.3, 120.1, 125.8, 127.4 (2 × C), 129.2 (2 × C), 129.75, 129.83, 131.5, 140.1, 146.5, 148.7, 154.6, 156.6, 161.6. IR (KBr): 3418, 3402, 1643, 1634, 1584, 1408, 1348, 1169 cm^{-1}. EIMS m/z: 333 (21), 332 (M^+, 100), 331 (13), 321 (10), 308 (11), 306 (29), 286 (11), 271 (30), 77 (31). HRMS (EI) m/z: $[M]^+$

calcd for $C_{17}H_{12}N_6O_2$: 332.1022; Found 332.1016.

*6-Amino-1-benzyl-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2k**).* The standard procedure involved the treatment of *N'*-(1-benzyl-4-formyl-3-phenyl-1*H*-pyrazol-5-yl)-*N*,*N*-di-methyl-methanimidamide (**1k**, 103 mg, 0.31 mmol, 1.0 equiv) with cyanamide (39.2 mg, 0.93 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2k**; 73% yields (68.2 mg), light yellow solid; mp 177–179 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (br, 2H), 5.50 (s, 2H), 7.22–7.34 (m, 5H), 7.37–7.41 (m, 1H), 7.46 (t, J = 7.44 Hz, 2H), 7.88–7.90 (m, 2H), 8.98 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 50.0, 107.2, 127.0 (2 × C), 127.67, 127.74 (2 × C), 128.6 (2 × C), 128.98, 128.93 (2 × C), 132.4, 136.7, 144.6, 154.0, 156.0, 161.3. IR (KBr): 3471, 3308, 3186, 1634, 1599, 1466, 1417, 1260 cm^{-1}. EIMS m/z: 302 (17), 301 (M^+, 100), 300 (56), 224 (29), 140 (29), 91 (81). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{15}N_5$: 301.1327; Found 301.1330.

*6-Amino-3-tert-butyl-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2l**).* The standard procedure involved the treatment of *N'*-[4-formyl-3-*t*-butyl-1-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanimidamide (**1l**, 98.5 mg, 0.33 mmol, 1.0 equiv) with cyanamide (41.6 mg, 0.99 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under

reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2l**; 74% yields (65.3 mg), light-yellow solid; mp 143–144 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.50 (s, 9H), 5.20 (br, 2H), 7.21–7.25 (m, 1H), 7.44–7.47 (m, 2H), 8.16 (dd, *J* = 8.60, 1.1 Hz, 2H), 8.88 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 30.0 (3 × C), 34.3, 108.4, 120.9 (2 × C), 125.6, 128.9 (2 × C), 139.1, 154.3, 155.4, 155.7, 161.1. IR (KBr): 3335, 3211, 2965, 1667, 1609, 1557, 1502, 1418, 1194, 1047 cm^{-1}. EIMS m/z: 267 (M^+, 48), 253 (18), 252 (100), 77 (11). HRMS (EI) m/z: $[M]^+$ calcd for $C_{15}H_{17}N_5$: 267.1484; Found 267.1487.

*6-Amino-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2m**).* The standard procedure involved the treatment of *N′*-[3-(4-chlorophenyl)-4-formyl-1-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methanim idamide (**1m**, 98.8 mg, 0.28 mmol, 1.0 equiv) with cyanamide (35.3 mg, 0.84 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2m**; 64% yields (57.7 mg), white solid; mp 223–224 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.33 (br, 2H), 7.30 (t, *J* = 7.42 Hz, 1H), 7.48–7.51 (m, 4 H), 7.92 (d, *J* = 8.15 Hz, 2H), 8.21 (d, *J* = 8.02 Hz, 2H), 9.02 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 108.4, 121.2 (2 × C), 126.3, 128.4 (2 × C), 129.0 (2 × C), 129.3 (2 × C), 130.5, 135.2, 138.8, 144.3, 154.0, 155.9, 161.5. IR (KBr): 3478, 3306, 3194, 1626, 1597, 1556, 1514, 1468, 1410, 1273, 1165, 1002 cm^{-1}. EIMS m/z: 323 (M^+ + 2, 34), 322 (31), 321 (M^+, 100), 320 (30), 306 (26), 297 (15), 271 (24), 91 (16), 77 (27). HRMS (EI) m/z:

$[M]^+$ calcd for $C_{17}H_{12}N_5Cl$: 321.0781; Found 321.0790.

*6-Amino-3-(4-methoxylphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2n**).* The standard procedure involved the treatment of *N*′-[4-formyl-3-(4-methoxylphenyl)-1-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-metha nimidamide (**1n**, 115 mg, 0.29 mmol, 1.0 equiv) with cyanamide (36.6 mg, 0.87 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 8:2) to give pure **2n**; 73% yields (67.2 mg), yellow solid; mp 205–206 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.87 (s, 3H), 5.28 (br, 2H), 7.04 (dd, *J* = 6.85, 1.95 Hz, 2H), 7.28 (t, *J* = 7.43 Hz, 1H), 7.49 (t, *J* = 7.98 Hz, 2H), 7.92 (dd, *J* = 6.80, 2.02 Hz, 2H), 8.23 (d, *J* = 7.60 Hz, 2H), 9.01 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 55.4, 108.6, 114.5 (2 × C), 121.1 (2 × C), 124.7, 126.0, 128.5 (2 × C), 129.0 (2 × C), 139.0, 145.3, 154.2, 155.8 160.5, 161.4. IR (KBr): 3439, 3418, 2075, 1643, 1634, 1409 cm^{-1}. EIMS m/z: 318 (23), 317 (M^+, 100), 316 (11), 302 (32). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{15}N_5O$: 317.1277; Found 317.1267.

*6-Amino-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2o**).* The standard procedure involved the treatment of *N*′-[4-formyl-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazol-5-yl]-*N*,*N*-di-methyl-methani midamide (**1o**, 99.7 mg, 0.30 mmol, 1.0 equiv) with cyanamide (37.8 mg, 0.90 mmol, 3.0 equiv) methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the intermolecular heterocyclization was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL)

and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2o**; 72% yields (65.1 mg), yellow solid; mp 61–62 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.42 (s, 3H), 5.29 (br, 2H), 7.29–7.33 (m, 1H), 7.49 (t, *J* = 7.88 Hz, 2H), 7.56 (t, *J* = 8.58 Hz, 2H), 7.88 (d, *J* = 8.04 Hz, 2H), 8.23 (d, *J* = 8.04 Hz, 2H), 9.03 (s, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 21.4, 108.7, 121.2 (2 × C), 126.1, 127.1 (2 × C), 128.7, 129.0 (2 × C), 129.2, 129.7 (2 × C), 139.4, 145.6, 154.2, 155.8, 161.3. IR (KBr): 3439, 3401, 3304, 3105, 2918, 2849, 1713, 1634, 1585, 1410, 1236 cm^{-1}. EIMS m/z: 302 (19), 301 (M^+, 100), 300 (36), 77 (10). HRMS (EI) m/z: $[M]^+$ calcd for $C_{18}H_{15}N_5$: 301.1327; Found 301.1321.

*Gram-Scale Preparation of 6-Amino-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**2a**).* The standard procedure involved the treatment of *N*'-(4-formyl-1,3-diphenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethyl-methanimidamide (**1a**, 2.00 g, 6.28 mmol, 1.0 equiv) with cyanamide (0.79 g, 18.9 mmol, 3.0 equiv) methanesulfonylchloride solution (25.0 mL) at 50–60 °C with 100 W of microwave energy for 1–2 h. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2a** (1.46 g, 81%).

Method C: Standard Procedure for Synthesis of 6-Aminopyrazolo[3,4-*d*]pyrimidines (2a–i). The reliable procedure involved the treatment of (**8a**–**i**, 1.0 equiv) with 3.0 equivalent of cyanamide ($NH_2C{\equiv}N$) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed (monitored by TLC), the

resulting mixture was added to water (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were washed with saturated sodium bicarbonate (2 × 15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by column chromatography on silica gel using CH_2Cl_2/ethyl acetate as eluent to give the corresponding 6-aminopyrazolo[3,4-*d*]pyrimidine products (**2a**–**i**) in 77–89% yields.

*6-Amino-1,3-diphenyl-1H-pyrazolo[3,4-d]pyrimidine (**2a**).* The standard procedure involved the treatment of 5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbaldehydes (**8a**, 84.1 mg, 0.32 mmol, 1.0 equiv) with cyanamide (39.5 mg, 0.94 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2a**; 87% yields (80.2 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.42 (br, 2H), 7.29 (t, *J* = 7.43 Hz, 1H), 7.44–7.54 (m, 5H), 7.98 (dd, *J* = 8.28, 1.28 Hz, 2H), 8.23 (dd, *J* = 8.60, 1.02 Hz, 2H), 9.04 (s, 1H).

*6-Amino-1-(2-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2b**).* The standard procedure involved the treatment of 5-amino-1-(2-methylphenyl)-1*H*-pyrazole-4-carbaldehydes (**8b**, 86.2 mg, 0.31 mmol, 1.0 equiv) with cyanamide (39.1 mg, 0.93 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel

(CH_2Cl_2/EtOAc = 19:1) to give pure **2b**; 84% yields (79.2 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (s, 3H), 5.39 (br, 2H), 7.34–7.40 (m, 3H), 7.43–7.46 (m, 2H), 7.48–7.52, (m, 2H), 7.96 (d, *J* = 7.04 Hz, 2H), 9.06 (s, 1H).

*6-Amino-1-(3-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2c**).* The standard procedure involved the treatment of 5-amino-1-(3-methylphenyl)-1*H*-pyrazole-4-carbaldehydes (**8c**, 92.3 mg, 0.33 mmol, 1.0 equiv) with cyanamide (41.6 mg, 0.99 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2c**; 81% yields (81.3 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.45 (s, 3H), 5.39 (br, 2H), 7.11 (d, *J* = 7.80 Hz, 1H), 7.37 (t, *J* = 7.80, 1H), 7.42–7.46 (m, 1H), 7.49–7.53 (m, 2H), 7.97 (d, *J* = 1.00 Hz, 1H), 7.99 (s, 2H), 8.02 (d, *J* = 8.20 Hz, 1H), 9.04 (s, 1H).

*6-Amino-1-(4-methylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2d**).* The standard procedure involved the treatment of 5-amino-1-(4-methylphenyl)-1*H*-pyrazole-4-carbaldehydes (**8d**, 97.3 mg, 0.35 mmol, 1.0 equiv) with cyanamide (44.2 mg, 1.05 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 19:1) to give pure **2d**; 89% yields (94.3 mg); ^{1}H NMR ($CDCl_3$, 400

MHz): δ 2.39 (s, 3H), 5.90 (br, 2H), 7.29 (d, *J* = 8.32 Hz, 2H), 7.46–7.53 (m, 3H), 7.94 (dd, *J* = 1.32, 8.20 Hz, 2H), 8.01 (d, *J* = 8.48 Hz, 2H), 9.01 (s, 1H).

*6-Amino-1-(2-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2e**).* The standard procedure involved the treatment of 5-amino-1-(2-chlorophenyl)-1*H*-pyrazole-4-carbaldehydes (**8e**, 98.0 mg, 0.33 mmol, 1.0 equiv) with cyanamide (42.1 mg, 0.99 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 9:1) to give pure **2e**; 77% yields (82.2 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.33 (br, 2H), 7.42–7.46 (m, 3H), 7.49–7.52 (m, 2H), 7.56–7.60 (m, 2H), 7.95–7.97 (m, 2H), 9.06 (s, 1H).

*6-Amino-1-(3-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine (**2f**).* The standard procedure involved the treatment of 5-amino-1-(3-chlorophenyl)-1*H*-pyrazole-4-carbaldehydes (**8f**, 92.4 mg, 0.31 mmol, 1.0 equiv) with cyanamide (39.1 mg, 0.93 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 8:2) to give pure **2f**; 84% yields (84.3 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.39 (br, 2H), 7.40 (t, *J* = 8.13 Hz, 1H), 7.46–7.54 (m, 4H), 7.94 (d, *J* = 7.12 Hz, 2H), 8.24 (d, *J* = 8.20 Hz, 1H) 8.37 (t, *J* = 1.94 Hz, 1H), 9.04 (s, 1H).

6-Amino-1-(4-chlorophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2g)****.* The standard procedure involved the treatment of 5-amino-1-(4-chlorophenyl)-1*H*-pyrazole-4-carbaldehydes (**8g**, 86.2 mg, 0.29 mmol, 1.0 equiv) with cyanamide (37.2 mg, 0.87 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 2:8) to give pure **2g**; 86% yields (80.3 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.30 (br, 2H), 7.44–7.48 (m, 3H), 7.52 (t, *J* = 7.34 Hz, 2H), 7.97 (d, *J* = 7.08 Hz, 2H), 8.25 (d, *J* = 8.88 Hz, 2H), 9.05 (s, 1H).

6-Amino-1-(4-bromophenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2h)****.* The standard procedure involved the treatment of 5-amino-1-(4-bromophenyl)-1*H*-pyrazole-4-carbaldehydes (**8h**, 103 mg, 0.30 mmol, 1.0 equiv) with cyanamide (80.2 mg, 0.90 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 8:2) to give pure **2h**; 83% yields (91.0 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (br, 2H), 7.46–7.53 (m, 3H), 7.59 (dd, *J* = 6.96, 1.92 Hz, 2H), 7.96 (dd, *J* = 7.04 Hz, 2H), 8.20 (dd, *J* = 6.96, 1.93 Hz, 2H), 9.04 (s, 1H).

6-Amino-1-(4-methoxylphenyl)-3-phenyl-1H-pyrazolo[3,4-d]pyrimidine ***(2i)****.* The standard procedure involved the treatment of

5-amino-1-(4-methoxylphenyl)-1*H*-pyrazole-4-carbaldehydes (**8i**, 94.1 mg, 0.30 mmol, 1.0 equiv) with cyanamide (40.4 mg, 0.96 mmol, 3.0 equiv) in methanesulfonylchloride solution (5.0 mL) at 50–60 °C with 100 W of microwave energy for 50 min. When the reaction was completed, the resulting mixture was added to saturated sodium bicarbonate (15 mL) and extracted with dichloromethane (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, then the residue was purified by chromatography on silica gel (CH_2Cl_2/EtOAc = 17:3) to give pure **2i**; 79% yields (80.1 mg); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.85 (s, 3H), 5.36 (br, 2H), 7.02 (d, *J* = 9.04 Hz, 2H), 7.45 (d, *J* = 7.16 Hz, 1H), 7.49–7.53 (m, 2H), 7.97 (d, *J* = 7.20 Hz, 2H), 8.04 (d, *J* = 9.08 Hz, 2H), 9.03 (s, 1H).

Standard Procedure for the Synthesis of 5-Amino-4-formylpyrazoles (8a–i).[39] A solution of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines (**1a–i**, 5.00 mmol, 1.0 equiv) and NaOH (10.0 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel using Hexane/ethyl acetate as eluent to give the corresponding 5-amino-4-formylpyrazole products (**8a–h**) in 83–96% yields.

*5-Amino-1,3-diphenyl-1H-pyrazole-4-carbaldehyde (**8a**)* It was obtained in 91% yield as a brown solid (1.20 g); mp 152–153 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.97 (br, 2H), 7.40–7.48 (m, 4H), 7.53 (t, *J* = 7.85 Hz, 2H), 7.58–7.60 (m, 2H), 7.70 (2H, dd, *J* = 9.85, 1.55 Hz), 9.86 (s, 1H).[39]

*5-Amino-1-(2-methylphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8b**)* A solution of *N*′-[1-(2-methylphenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi

damide (**1b**, 1.66 g, 5.00 mmol, 1.0 equiv) and NaOH (0.40 g, 10.0 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 7:3) to give pure **8b**; 83% yields (1.15 g), light yellow solid; mp 118–119 °C (Hexane–EtOAc). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.22 (s, 3H), 5.67 (br, 2H), 7.30–7.46 (m, 7H), 7.70 (dd, *J* = 8.05, 1.47 Hz, 2H), 9.85 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 17.6, 103.9, 127.3, 127.7, 128.6 (2 × C), 128.7 (2 × C), 129.0, 130.2, 131.8 (C + CH), 134.8, 136.6, 150.7, 153.1, 185.3. IR (KBr): 3414, 3295, 3194, 1639, 1509, 1374, 774 cm^{-1}. EIMS m/z: 278 (19), 277 (M^+, 100), 276 (22), 248 (22), 145 (12), 128 (11), 104 (12). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{15}N_3O$: 277.1215; Found 277.1211.

*5-Amino-1-(3-methylphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8c**)* A solution of *N*′-[1-(3-methylphenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1c**, 1.70 g, 5.10 mmol, 1.0 equiv) and NaOH (0.41 g, 10.2 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8c**; 85% yields (1.20 g), brown solid; mp 107–109 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.41 (s, 3H), 5.97 (br, 2H), 7.22 (d, *J* = 7.43 Hz, 1H), 7.34–7.47 (m, 6H), 7.70 (dd, *J* = 7.90, 1.4 Hz, 2H), 9.84 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 21.4, 104.7, 120.8, 124.8, 128.6 (2 × C), 128.7 (2 × C), 129.1,

129.3, 129.6, 131.6, 136.8, 140.3, 149.9, 153.5, 185.4. IR (KBr): 3408, 3301, 3196, 3059, 2922, 2851, 1643, 1610, 1509, 1374, 772 cm^{-1}. EIMS m/z: 278 (17), 277 (M^+, 100), 276 (52), 157 (11), 128 (14), 91 (26), 77 (27). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{15}N_3O$: 277.1215; Found 277.1208.

*5-Amino-1-(4-methylphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8d**)* A solution of *N'*-[1-(4-methylphenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1d**, 1.66 g, 5.00 mmol, 1.0 equiv) and NaOH (0.40 g, 10.0 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 7:3) to give pure **8d**; 92% yields (1.28 g), yellow solid; mp 134–135 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 2.41 (s, 3H), 5.91 (br, 2H), 7.32 (d, *J* = 8.04 Hz, 2H), 7.41–7.47 (m, 5H), 7.69 (dt, *J* = 6.20, 1.66 Hz, 2H), 9.85 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 21.2, 104.7, 124.0 (2 × C), 128.6 (2 × C), 128.7 (2 × C), 129.1, 130.5 (2 × C), 131.7, 134.3, 138.7, 149.9, 153.3, 185.4. IR (KBr): 3410, 3301, 3192, 2824, 1640, 1529, 1510, 1375, 772 cm^{-1}. EIMS m/z: 277 (18), 277 (M^+, 100), 276 (46). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{15}N_3O$: 277.1215; Found 277.1213.

*5-Amino-1-(2-chlorophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8e**)* A solution of *N'*-[1-(2-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1d**, 1.73 g, 4.90 mmol, 1.0 equiv) and NaOH (0.39 g, 9.80 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated

$NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8e**; 84% yields (1.23 g), yellow solid; mp 128–129 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.79 (br, 2H), 7.41–7.46 (m, 5H), 7.52–7.54 (m, 1H), 7.56–7.58 (m, 1H), 7.70 (dd, *J* = 8.00, 1.56 Hz, 2H), 9.85 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 103.9, 128.3, 128.6 (2 × C), 128.7 (2 × C), 129.1, 130.0, 130.9, 131.3, 131.5, 132.2, 133.9, 151.1, 153.7, 185.3. IR (KBr): 3412, 3293, 3196, 2834, 1643, 1511, 1374 cm^{-1}. EIMS m/z: 299 (M^+ + 2, 34), 298 (36), 297 (M^+, 100), 296 (53), 177 (11), 128 (12), 77 (13). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{12}ClN_3O$: 297.0669; Found 297.0674.

*5-Amino-1-(3-chlorophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8f**)* A solution of *N′*-[1-(3-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1f**, 1.76 g, 5.00 mmol, 1.0 equiv) and NaOH (0.40 g, 10.0 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8f**; 87% yields (1.30 g), white solid; mp 117–119 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.06 (br, 2H), 7.37 (dd, *J* = 7.95, 1.19 Hz, 1H), 7.42–7.50 (m, 5H), 7.64 (t, *J* = 1.90 Hz, 1H), 7.68 (dd, *J* = 7.85, 1.56 Hz, 2H), 9.83 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 104.8, 121.6, 124.2, 128.5, 128.6 (2 × C), 128.8 (2 × C), 129.3, 130.8, 131.3, 135.7, 138.1, 150.0, 153.8, 185.5. IR (KBr): 3405, 3292, 2922, 1622, 1509, 1486, 1374, 777 cm^{-1}. EIMS m/z: 299 (M^+ + 2, 31), 298 (34), 297 (M^+, 100), 296 (55), 128 (13), 111 (12), 77 (16). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{12}ClN_3O$: 297.0669; Found 297.0674.

*5-Amino-1-(4-chlorophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8g**)* A solution of *N*′-[1-(4-chlorophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1g**, 1.73 g, 4.90 mmol, 1.0 equiv) and NaOH (0.39 g, 9.80 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8g**; 89% yields (1.30 g), white solid; mp 107–108 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.00 (br, 2H), 7.42–7.49 (m, 5H), 7.53 (dd, *J* = 6.66, 2.19 Hz, 2H), 7.67 (dd, *J* = 7.90, 1.60 Hz, 2H), 9.82 (s, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ 104.8, 125.1 (2 × C), 128.5 (2 × C), 128.8 (2 × C), 129.2, 130.0 (2 × C), 131.3, 134.1, 135.4, 149.9, 153.7, 158.4. IR (KBr): 3401, 3299, 3201, 2924, 1644, 1494, 1375, 772 cm^{-1}. EIMS m/z: 299 (M^+ + 2, 35), 298 (35), 297 (M^+, 100), 296 (51), 77 (10). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{12}ClN_3O$: 297.0669; Found 297.0663.

*5-Amino-1-(4-bromophenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8h**)* A solution of *N*′-[1-(4-bromophenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimi damide (**1h**, 2.03 g, 5.10 mmol, 1.0 equiv) and NaOH (0.41 g, 10.2 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8h**; 91% yields (1.59 g), brown solid; mp 131–133 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.00 (br, 2H), 7.43–7.49 (m, 5H), 7.64 (dd, *J* = 6.73, 2.02 Hz, 2H), 7.68 (dd, *J* = 7.90, 1.62 Hz, 2H), 9.83 (s, 1H). ^{13}C{^{1}H} NMR (125

MHz, $CDCl_3$): δ 104.8, 122.1, 125.3 (2 × C), 128.5 (2 × C), 128.8 (2 × C), 129.2, 131.3, 133.0 (2 × C), 136.0, 149.9, 153.7, 158.5. IR (KBr): 3398, 3287, 2826, 1643, 1509, 1491, 1375, 771 cm^{-1}. EIMS m/z: 344 (17), 343 (M^+ + 2, 100), 342 (59), 341 (M^+, 98), 340 (41), 128 (11), 77 (15). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{16}H_{12}BrN_3O$: 341.0164; Found 341.0162.

*5-Amino-1-(4-methoxylphenyl)-3-phenyl-1H-pyrazole-4-carbaldehyde (**8i**)* A solution of

N'-[1-(4-methoxylphenyl)-4-formyl-3-phenyl-1*H*-pyrazol-5-yl-*N*,*N*-dimethyl-methanimidamide (**1i**, 1.74 g, 5.00 mmol, 1.0 equiv) and NaOH (0.40 g, 10.0 mmol, 2.0 equiv) in MeOH solution (45 mL) at reflux within 2–3 h. When the reaction was completed, the reaction mixture was concentrated to remove solvent, added to water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were washed with saturated $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue solution was purified by short column chromatography on silica gel (hexane/EtOAc = 6:4) to give pure **8i**; 96% yields (1.41 g), light yellow solid; mp 109–111 °C. ^1H NMR ($CDCl_3$, 500 MHz): δ 3.84 (s, 3H), 5.86 (br, 2H), 7 01 (dd, *J* = 6.78, 2.18 Hz, 2H), 7.41–7.47 (m, 5H), 7.69 (dt, *J* = 6.30, 1.64 Hz, 2H), 9.83 (s, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 55.6, 104.5, 115.1 (2 × C), 125.9 (2 × C), 128.6 (2 × C), 128.7 (2 × C), 129.0, 129.5, 131.6, 150.0, 153.1, 159.7, 185.4. IR (KBr): 3413, 3312, 3196, 2837, 1640, 1529, 1509, 1249 cm^{-1}. EIMS m/z: 294 (20), 293 (M^+, 100), 292 (31). HRMS (EI) m/z: $[M]^+$ Calcd for $C_{17}H_{15}N_3O_2$: 293.1164; Found 293.1169.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Copies of ^{1}H NMR spectra of compounds **1a**, **1c**, **1d**, **1e**–**f**, **1g**, **1h**–**j**, and **1l**–**o**, and **8a** and ^{1}H and ^{13}C NMR spectra of compounds **1b**, **1k**, **2a**–**o** and **8b**–**i** (PDF)

X-ray data for compound **2c** (CCDC 1945863) (CIF)

AUTHOR INFORMATION

Corresponding Authors

*E-mail: wongfungfuh@yahoo.com.tw; ffwong@mail.cmu.edu.tw.

ORCID

Fung Fuh Wong: 0000-0002-0012-1238

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the Ministry of Science and Technology, Taiwan (MOST 107-2113-M-039-006) for financial support.

REFERENCES

(1) Bonn, P.; Brink, D. Mikael Fägerhag, J.; Jurva, U.; Robb, G. R.; Schnecke, V.; Henriksson, A. S.; Waring, M. J.; Westerlund, C. The Discovery of a Novel Series of Glucokinase Activators Based on a Pyrazolopyrimidine Scaffold. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7302–7305.

(2) Bakavoli, M.; Bagherzadeh, G.; Vaseghifar, M.; Shiri, A.; Mehdi Pordel, M.; Mashreghi, M.; Pordeli, P.; Araghi, M. Molecular Iodine Promoted Synthesis of New Pyrazolo[3,4-*d*]pyrimidine Derivatives as Potential Antibacterial Agents. *Eur. J. Med. Chem.* **2010**, *45*, 647–650.

(3) Holla, B. S.; Mahalinga, M.; Karthikeyan, M. S.; Akberali, P. M.; Shetty, N. S. Synthesis of Some Novel Pyrazolo[3,4-*d*]pyrimidine Derivatives as Potential Antimicrobial Agents. *Bioorg. Med. Chem.* **2006**, *14*, 2040–2047.

(4) Shamroukh, A. H.; Rashad, A. E.; Sayed, H. H. Synthesis of Some Pyrazolo[3, 4]pyrimidine Derivatives for Biological Evaluation. *Phosphorous, Sulfur and Silicon and the Related Elements* **2005**, *180*, 2347–2360.

(5) Rigueiroa, F.; Teixeiraa, S.; Salaheldinb, A. M.; Oliveira-Camposb, A. M. F.; Rodriguesb, L. M.; Peixotoc, F.; Oliveira, M. M. S10.17 Evaluation of Antioxidant Properties of Some Pyrazolo[3,4-*d*]pyrimidines Derivatives and their Effectson Mitochondria Bioenergetics. *Biochimica et Biophysica Acta (BBA) - Bioenergetics* **2008**, *1777*, S62.

(6) (a) Kumar, A.; Ahmad, I.; Chhikara, B. S.; Tiwari, R.; Mandal, D.; Parang, K. Synthesis of 3-Phenylpyrazolopyrimidine-1,2,3-triazole Conjugates and Evaluation of Their Src Kinase Inhibitory and Anticancer Activities. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1342–1346. (b) Ghorab, M. M.; Ragab, F. A.; Alqasoumi, S. I.; Alafeefy, A. M.; Aboulmag, S. A. Synthesis of Some New Pyrazolo[3,4-*d*]pyrimidine Derivatives of Expected Anticancer and Radioprotective Activity. *Eur. J. Med. Chem.* **2010**, *45*, 171–178.

(7) Liu, H.; Wang, H. Q.; Liu, Z. J. Synthesis and Herbicidal Activity of Novel Pyrazolo[3,4-*d*]pyrimidin-4-one Derivatives Containing Aryloxyphenoxypropionate Moieties. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2203–2209.

(8) (a) Chern, J. H.; Shia, K. S.; Hsu, T. A.; Tai, C. L.; Lee, C. C.; Lee, Y. C.; Chang, C. S.; Tseng, S. N.; Shih, S. R. Design, Synthesis, and Structure–activity Relationships of Pyrazolo[3,4-*d*]pyrimidines: a Novel Class of Potent Enterovirus Inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2519–2525. (b) Rashad, A. E.; Hegab, M. I.; Abdel-Megeid, R. E.; Fathalla, N.; Abdel-Megeid, F. M. E. Synthesis and Anti-HSV-1 Evaluation of Some Pyrazoles and Fused Pyrazolopyrimidines. *Eur. J. Med. Chem.* **2009**, *44*,

3285–3292.

(9) Quintela, J. M.; Peinador, C.; González, L.; Devesa, I.; Ferrándiz, M. L.; Alcaraz, M. J.; Riguera, R. 6-Dimethylamino 1*H*-Pyrazolo[3,4-*d*]pyrimidine Derivatives as New Inhibitors of Inflammatory Nediators in Intact Cells. *Bioorg*. *Med*. *Chem*. **2003**, *11*, 863–868.

(10) (a) Avasthi, K.; Farooq, S. M.; Raghunandan, R.; Ma, P. R. Design and Synthesis of Pyrazolo[3,4-*d*]pyrimidine Core Based Dissymmetrical 'Leonard linker' Compounds: ^{1}H NMR and Crystallographic Evidence for Folded Conformation due to Arene Interactions. *J*. *Mol*. *Struc*. **2006**, *785*, 106–113. (b) Venkatesan, G.; Paira, P.; Cheong, L. C.; Vamsikrishna, K.; Federico , S.; Klotz, K.-N.; Spalluto, G.; Pastorin, G. Discovery of Simplified N^2-substituted Pyrazolo[3,4-*d*]pyrimidine Derivatives as Novel Adenosine Receptor Antagonists: Efficient Synthetic Approaches, Biological Evaluations and Molecular Docking Studies. *Bioorg*. *Med*. *Chem*. **2014**, *22*, 1751–1765.

(11) Zhang, L.; Fan, J.; Chong, J.-H.; Cesena, A.; Tam, B. Y. Y.; Gilson, C.; Boykin, C.; Wang, D.; Aivazian, D.; Marcotte, D.; Xiao, G.; Le Brazidec, J.-Y.; Piao, J.; Lundgren, K.; Hong, K.; Vu, K.; Nguyen, K.; Gan, L.-S.; Silvian, L.; Ling, L.; Teng, M.; Reff, M.; Takeda, N.; Timple, N.; Wang, Q.; Morena, R.; Khan, S.; Zhao, S.; Li, T.; Lee, W.-C.; Taveras, A. G.; Chao, J. Design, Synthesis, and Biological Evaluation of Pyrazolopyrimidine-sulfonamides as Potent Multiple-mitotic Kinase (MMK) Inhibitors (Part I). *Bioorg*. *Med*. *Chem*. *Lett*. **2011**, *21*, 5633–5637.

(12) Lim, S. M.; Xie, T.; Westover, K. D.; Ficarro, S. B.; H Tae, H. S.; Gurbani, D.; Sim, T.; Marto, J. A.; Janne, P. A.; Crews, C. M.; Gray, N. S. Development of Small Molecules Targeting the Pseudokinase Her3. *Bioorg*. *Med*. *Chem*. *Lett*. **2015**, *25*, 3382–3389.

(13) (a) Canyuk, B.; Medrano, F. J.; Wenck, M. A.; Focia, P. J.; Eakin, A. E.; Craig III, S. P. Interactions at the Dimer Interface Influence the Relative Efficiencies for Purine Nucleotide Synthesisand Pyrophosphorolysis in a Phosphoribosyltransferase. *J. Mol. Biol.* **2004**, *335*, 905–921. (b) Seela, F.; Xu, K. Pyrazolo[3,4-*d*]pyrimidineribonucleosides Related to 2-Aminoadenosine and Isoguanosine: Synthesis, Deamination and Tautomerism. *Org. Biomol. Chem.* **2007**, *5*, 3034–3045.

(14) Abdelazeem, A. H.; Abdelatef , S. A.; El-Saadi , M. T.; Omar, H. A.; Khan, S. I.; McCurdy, C. R.; El-Moghazy, S. M. Novel Pyrazolopyrimidine Derivatives Targeting COXs and iNOS enzymes; Design, Synthesis and Biological Evaluation as Potential Anti-inflammatory Agents. *Eur. J. Pharmacol. Sci.* **2014**, *62*, 197–211.

(15) Quintela, J. M.; Peinador, C.; Moreira, M. J.; Alfonso, A.; Botana, L. M.; Riguera, R. Pyrazolopyrimidines: Synthesis, Effect on Histamine Release from Rat Peritoneal Mast Cells and Cytotoxic Activity. *Eur. J. Med. Chem.* **2001**, *36*, 321–332.

(16) (a) Brazidec, J.-Y.; Pasis, A.; Tam, B.; Boykin, C.; Black, C.; Wang, D.; Claassen, G.; Chong, J.-H.; Cha, J.; Fan, J.; Nguyen, K.; Silvian, L.; Ling, L.; Zhang, L.; Choi, M.; Teng, M.; Pathan, N.; Zhao, S.; Li, T.; Taveras, A. Synthesis, SAR and Biological Evaluation of 1,6-Disubstituted-1*H*-pyrazolo[3,4-*d*]pyrimidines as Dual Inhibitors of Aurora Kinases and CDK1. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2070–2074. (b) Brazidec, J.-Y.; Pasis, A.; Tam, B.; Boykin, C.; Wang, D.; Marcotte, D. J.; Claassen, G.; Chong, J.-H.; Chao, J.; Fan, J.; Nguyen, K.; Silvian, L.; Ling, L.; Zhang, L.; Choi, M.; Teng, M.; Pathan, N.; Zhao, S.; Li, T.; Taveras, A. Structure-based Design of 2,6,7-Trisubstituted-7*H*-pyrrolo[2,3-*d*]pyrimidines as

Aurora Kinases Inhibitors. *Bioorg*. *Med*. *Chem*. *Lett*. **2012**, *22*, 4033–4037.

(17) Girardet, J.-L.; Koh, Y.-H.; An, H.; Hong, Z. Cytidine Analogs and Method of Use. WO **2004** 080466A1.

(18) Woller, K. R.; Curtin, M. L.; Frank, K. E.; Josephsohn, N. S.; Li, B. C.; Wishart, N. Novel Pyrazolo[3,4-*d*]pyrimidine Compounds. WO **2011** 156698A2.

(19) (a) Seela, F.; Steker, H. Synthesis of the β-D-Deoxyribofuranoside of 6-Amino-1*H*-pyrazolo[3,4-*d*]pyrimidin-4(5*H*)-one — A New Isoster of 2'-Deoxyguanosine. *Heterocycles* **1985**, *23*, 2521– 2524. (b) Wainwright, P.; Maddaford, A.; Simms, M.; Forrest, N.; Glen, R.; Hart, J.; Zhang, X.; Pryde, D. C.; Stephenson, P. T.; Middleton, D. S. Guyot, T; Sutton, S. C. Synthesis of Novel 2-Cyano-7-deaza-8-azapurine- and 2-Cyano-8-azapurine-derived Nucleosides. *Synlett* **2011**, 1900–1904.

(20) (a) Lyu, W.; Ma, L. J.; Jin, J.; Xiao, D. H.; Zho, S. L. Preparation Method of Pharmaceutical Intermediate *N*-Arylquinazolinyl-amine Compounds. CN **2016** 105669566A. (b) Lim, F. P. L.; Luna, G.; Dolzhenko, A. V. A One-Pot, Three-component, Microwave-assisted Synthesis of Novel 7-Amino-substituted 4-aminopyrazolo[1,5-*a*][1,3,5]triazine-8-carbonitriles. *Tetrahedron Lett.* **2015**, *56*, 7016–7019.

(21) (a) Jobst, K. J.; Gerbaux, P.; Dimopoulos-Italiano, G.; Ruttink, P. J. A.; Terlouw, J. The Quest for the Elusive Carbodiimide Ion $HN=C=NH^{\cdot+}$ and its Generation from Ionized Cyanamide by Proton-transport Catalysis. *Chem*. *Phys*. *Lett*. **2009**, *478*, 144–149. (b) Yin, P.; Ma, W.-B.; Chen, Y.; Huang, W.-C.; Deng, Y.; He, L. Highly Efficient Cyanoimidation of Aldehydes. *Org. Lett.* **2009**, *11*, 5482–5485.

(22) Belsky, A. J.; Li, T.-J.; Brill, T. B. Reactions of Cyanamide, Dicyandiamide and Related Cyclic Azines in High Temperature Water. *J. Supercritical. Fluids.*

1997, *10*, 201–208.

(23) (a) Castagnolo, D.; Schenone, S.; Botta, M. Guanylated Diamines, Triamines, and Polyamines: Chemistry and Biological Properties. *Chem. Rev.* **2011**, *111*, 5247–5300. (b) Chen, C.-Y.; Lin, H.-C.; Huang, Y.-Y.; Huang, J.-J.; Yeh, M.-Y., Wong, F. F. 'One-flask' Transformation of Isocyanates and Isothiocyanates to Guanidines Hydrochloride by Using Sodium Bis(trimethylsilyl)amide. *Tetrahedron* **2010**, *66*, 1892–1897.

(24) Mancheño, O. G.; Bistri, O.; Bolm, C. Iodinane- and Metal-Free Synthesis of *N*-Cyano Sulfilimines: Novel and Easy Access of NH-Sulfoximines. *Org. Lett.* **2007**, *9*, 3809–3811.

(25) Kamo, T.; Endo, M.; Sato, M.; Kasahara, R.; Yamaya, H.; Hiradate, S.; Fujii, Y.; Hirai, N.; Hirota, M. Limited Distribution of Natural Cyanamide in Higher Plants: Occurrence in Vicia Villosa Subsp. Varia, V. Cracca, and Robinia Pseudo-acacia. *Phytochemistry* **2008**, *69*, 1166–1172.

(26) Koketsu, M.; Fukuta Y.; Ishihara, H. Preparation of *N*,*N*-Unsubstituted Selenoureas and Thioureas from Cyanamides. *Tetrahedron Lett.* **2001**, *42*, 6333–6335.

(27) Hua, G.; Zhang, Q.; Li, Y.; Slawin, A. M. Z.; Woollins, J. D. Novel Heterocyclic Selenazadiphospholaminediselenides, Zwitterionic Carbamidoyl(phenyl)-phosphinodiselenoic Acids and Selenoureas Derived from Cyanamides. *Tetrahedron* **2009**, *65*, 6074–6082.

(28) Wu, Y.-Q.; Limburg, D. L.; Wilkinson, D. E.; Hamilton, G. S. 1-Cyanoimidazole as a Mild and Efficient Electrophilic Cyanating Agent. *Org. Lett.* **2000**, *2*, 795–797.

(29) Guo, X.; Chen, W.; Chen, B.; Huang, W.; Qi, W.; Zhang, G.; Yu, Y. One-Pot Three-component Strategy for Functionalized 2-Aminoimidazoles via Ring

Opening of α-Nitro Epoxides. *Org. Lett.* **2015**, *17*, 1157–1159.

(30) (a) Špulák, M.; Lubojacký, R.; Šenel, P.; Kuneš, J.; Pour, M. Direct C−H Arylation and Alkenylation of 1-Substituted Tetrazoles: Phosphine as Stabilizing Factor. *J. Org. Chem.* **2010**, *75*, 241–244. (b) Srinivas, D.; Ghule, V. D.; Muralidharan, K. Synthesis of Nitrogen-rich Imidazole, 1,2,4-Triazole and Tetrazole-based Compounds. *RSC Adv*. **2014**, *7*, 7041–7051.

(31) Dutta, S.; Higginson, C. J.; Ho, B. T.; Rynearson, K. D.; Dibrov, S. M.; Hermann, T. 1,3-Diazepanes of Natural Product-like Complexity from Cyanamide-induced Rearrangement of Epoxy-δ-lactams. *Org. Lett.*, **2010**, *12*, 360–363.

(32) Hulme, R.; Zamora, O. D. P.; Mota, E. J.; Pastén, M. A.; Contreras-Rojas, R.; Miranda, R.; Valencia-Hernöández, I.; Correa-Basurto, J.; Trujillo-Ferrara, J.; Delgado, F. Cyanamide: a Convenient Building Block to Synthesize 4-Aryl-2-cyanoimino-3,4-dihydro-1*H*-pyrimidine Systems via a Multicomponent Reaction. *Tetrahedron* **2008**, *64*, 3372–3380.

(33) Pchalek, K.; Hay, M. P. Stille Coupling Reactions in the Synthesis of Hypoxia-selective 3-Alkyl-1,2,4-benzotriazine 1,4-Dioxide Anticancer Agents. *J. Org. Chem.* **2006**, *71*, 6530–6535.

(34) Stephens, R. W.; Domeier, L. A.; Todd, M. G.; Nelson, V. A. *N*-Cyanoimides: Reactivity Studies with Amine Nucleophiles. *Tetrahedron Lett*. **1992**, *33*, 733.

(35) Beshore, D. C.; Dinsmore, C. J. Efficient Synthesis of Unsymmetrical 1,4-Disubstituted-2,3-diketopiperazines via Tandem Reductive Amination–cyclization. *Tetrahedron Lett*. **2000**, *41*, 8735–8739.

(36) Tsai, A.-E.; Yen, W.-P.; Tseng, C.-C.; Xie, J.-J.; Liou, M.-Y.; Li, Y.-T.; Uramaru, N.; Wong, F. F. Efficient Acid Catalytic Synthesis of Pyrazolopyrimidines from 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines with Cyanamide. *Tetrahedron*

2018, *74*, 2787–2791.

(37) (a) Mavandadi, F.; Lidström, P. *Curr*. Microwave-assisted Chemistry in Drug Discovery. *Top*. *Med*. *Chem*. **2004**, *4*, 773–792. (b) Appukkuttan, P.; Mehta, V. P.; Van der Eycken, E. V. Microwave-assisted Cycloaddition Reactions. *Chem*. *Soc*. *Rev*. **2010**, *39*, 1467–1477. (c) Sharma, A.; Appukkuttan, P.; Van der Eycken, E. V. Microwave-assisted Synthesis of Medium-sized Heterocycles. *Chem*. *Commun*. **2012**, 1623–1637. (d) Bui, H. T. B.; Ha, Q. T. K.; Oh, W. K.; Vo, D. D.; Chau, Y. N. T.; Tu, C. T. K.; Em Pham, C.; Tran, P. T.; Tran, L. T.; Ma, H. V. Microwave-assisted Synthesis and Cytotoxic Activity Evaluations of New Benzimidazole Derivatives. *Tetrahedron Lett*. **2016**, *57*, 887–891. (e) Dallinger, D.; Irfan, M.; Suljanovic, A.; and Kappe, C. O. An Investigation of Wall Effects in Microwave-Assisted Ring-Closing Metathesis and Cyclotrimerization Reactions. *J. Org. Chem.* **2010**, *75*, 5278–5288.

(38) Castillo, J.-C.; Estupiñan, D.; Nogueras, M.; Cobo, J.; Portilla, J. 6-(Aryldiazenyl)pyrazolo[1,5-*a*]pyrimidines as Strategic Intermediates for the Synthesis of Pyrazolo[5,1-*b*]purines. *J. Org. Chem.*, **2016**, *81*, 12364–12373.

(39) Cheng, K.-M.; Huang, Y.-Y.; Huang, J.-J.; Kaneko, K.; Kimura, M.; Takayama, H.; Juang, S.-H.; Wong, F. F. Synthesis and Antiproliferative Evaluation of *N*,*N*-disubstituted-*N'*-[1-aryl-1*H*-pyrazol-5-yl]-methnimidamides. *Bioorg*. *Med*. *Chem*. *Lett*. **2010**, *20*, 6781–6784.

(40) Wen, K.-S.; Lin, H.-Y.; Huang, Y.-Y.; Kaneko, K.; Takayama, H.; Kimura, M.; Juang, S.-H.; Wong, F. F. Chemoselective Synthesis, Antiproliferative Activities, and SAR Study of 1*H*-pyrazol-5-yl-*N*,*N*-dimethylformamidines and Pyrazolyl-2-azadienes. *Med*. *Chem*. *Res*. **2012**, *21*, 3920–3928.

(41) Simay, A.; Takacs, K.; Horvath, K.; Dvortsak, P. Vilsmeier-Haack Reaction of 5-Amino- and 5-Acylaminopyrazoles. *Acta Chimica Academiae Scientiarum*

Hungaricae **1980**, *105*, 127–139.

(42) (a) Huang, Y.-Y.; Wang, L.-Y.; Chang, C.-H.; Kuo, Y.-H.; Kaneko, K.; Takayama, H.; Kimura, M.; Juang, S.-H.; Wong, F. F. One-Pot Synthesis and Antiproliferative Evaluation of Pyrazolo[3,4-*d*]pyrimidine Derivatives. *Tetrahedron* **2012**, *68*, 9658–9664. (b) Chang, C.-H.; Tsai, H. J.; Huang, Y.-Y.; Lin, H.-Y.; Wang, L.-Y.; Wu, T.-S.; Wong, F. F. Selective Synthesis of Pyrazolo[3,4-*d*]pyrimidine, *N*-(1*H*-pyrazol-5-yl)formamide, or *N*-(1*H*-pyrazol-5-yl)formamidine Derivatives from *N*-1-substituted-5-aminopyrazoles with New Vilsmeier-type Reagents. *Tetrahedron* **2013**, *69*, 1378–1386. (c) Lu, S.-H.; Liu, P.-L.; Wong, F. F. Vilsmeier Reagent-mediated Synthesis of 6-[(Formyloxy)methyl]-pyrazolopyrimidines via a One-Pot Multiple Tandem Reaction. *RSC Advances* **2015**, *5*, 47098–47107.