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Microwave-assisted protocols for the expedited synthesis of pyrazolo[1,5-*a*] and [3,4-*d*]pyrimidines

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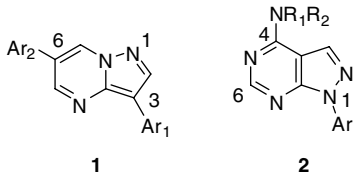
Abstract—General, high-yielding MAOS protocols for the expedited synthesis of functionalized pyrazolo[1,5-*a*]pyrimidines and pyrazolo[3,4-*b*]pyrimidines, as well as their pyrazole precursors, are described amenable to an iterative analogue library synthesis strategy for lead optimization.

In the course of our program in drug discovery, several high-throughput screens have identified pyrazolo[1,5-*a*]pyrimidines **1** and pyrazolo[3,4-*d*]pyrimidines **2** as lead compounds for both cancer and neuroscience programs (Fig. 1). While numerous reports describe the syntheses of **1** and **2**, though the latter is primarily in the patent literature, yields are typically moderate (<50%) with prolonged reaction times at high temperatures (steps requiring >48 h at reflux).[1–4] To employ an iterative analogue library synthesis approach for lead optimization, significant refinements were required in the synthetic protocols for **1** and **2**.

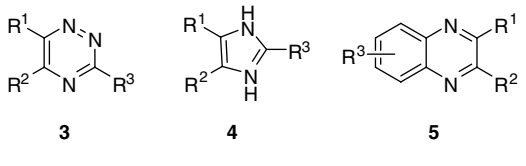
As many of the leads identified from HTS campaigns are small heterocyclic compounds, our laboratory has devoted significant effort to develop efficient protocols for the preparation of diverse heterocyclic templates employing microwave-assisted organic synthesis (MAOS).[5] In recent reports, we have described general, high-yielding MAOS protocols for the expedient synthesis of 1,2,4-triazines **3**,[6] imidazoles **4**,[7] quinoxalines **5**,[8] pyrazinone **6**,[9] 5-amniooxazoles **7**,[10] and quinoxalinones **8**[5] from simple starting materials (Fig. 2). Therefore, the application of MAOS to develop a general, high-yielding and expedient synthesis of pyrazolo[1,5-*a*]pyrimidines **1** and pyrazolo[3,4-*d*]pyrimidines **2** seem warranted.

Classical conditions for the synthesis of pyrazolo[1,5-*a*]-pyrimidines **1** involve refluxing a 5-amino-4-aryl-pyrazole **9** with a commercially available 2-arylmalondialdehyde **12** in ethanol with catalytic acetic acid for 24 h to deliver pyrazolo[1,5-*a*]pyrimidines **1** in



1 **2**

Figure 1. Generic structures of pyrazolo[1,5-*a*]pyrimidine **1** and pyrazolo[3,4-*b*]pyrimidine **2** screening leads.



3 **4** **5**

6 **7** **8**

Figure 2. Heterocyclic templates accessed through MAOS.

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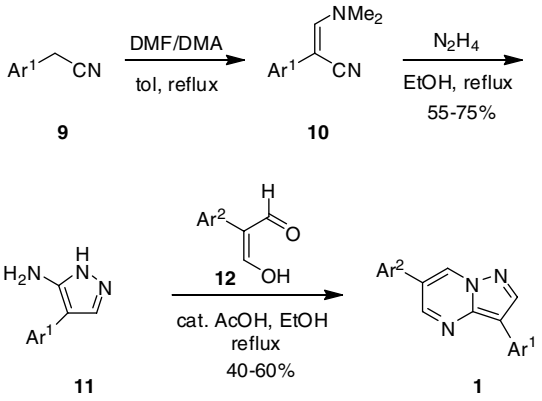
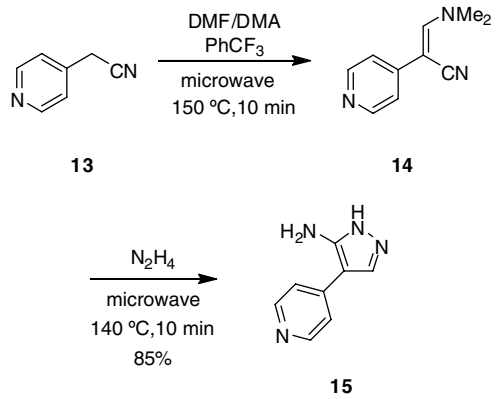


Scheme 1. Classical synthesis of pyrazolo[1,5-*a*]pyrimidines **1**.

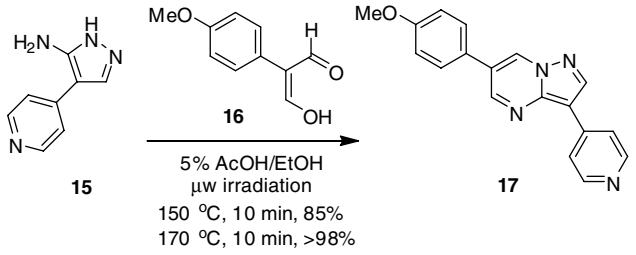
40–60% yield.[1,2] The starting 5-amino-4-arylpyrazoles **11** were prepared in two steps from the corresponding acetonitriles **9** by refluxing in DMF/DMA (dimethylformamide–dimethlyacetal) to afford **10**, followed by treatment with hydrazine in refluxing ethanol to afford **11** in 55–75% yield. The overall sequence required three overnight (72 h) reflux reactions[1,2] (Scheme 1).

Our attention first focused on improving the synthesis of the requisite starting 5-amino-4-arylpyrazoles **11**, as few of these analogs are commercially available, and those that can be purchased are expensive (~$100/g). To improve the synthesis, we employed MAOS. In the event, nitrile **13** was heated at 160 °C in DMF/DMA to afford complete conversion to **14** in 10 min, as judged by analytical LCMS. To the same microwave vial was added hydrazine via syringe and the vial heated again under microwave irradiation to 140 °C for 10 min to deliver the desired 5-amino-4-pyridylpyrazole **15** in 85% isolated yield (Scheme 2). This represents a significant improvement over the conventional thermal protocol that required 48 h of reaction time and 55–75% yield.[1,2] In a similar fashion, the 5-amino-4-phenylpyrazole was also prepared (88%).

Once **15** was in hand, conventional thermal conditions were quickly adapted and optimized on a single-mode microwave synthesizer. In the event, exposing aminopyrazole **15** and malondialdehyde **16** in 5% AcOH/



Scheme 2. MAOS synthesis of 5-amino-4-pyridylpyrazole **15**.

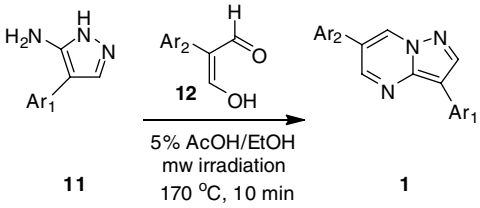


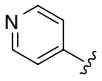
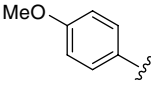
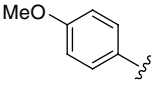
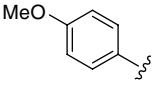
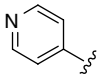
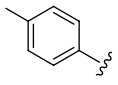
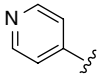
Scheme 3. MAOS synthesis of pyrazolo[1,5-*a*]pyrimidine **1**.

EtOH at 150 °C for 10 min afforded pyrazolo[1,5-*a*]pyrimidine **17**, one of our HTS leads, in 85% isolated yield (Scheme 3). Product **17** precipitated from solution upon the end-of-run rapid cooling to 40 °C in the microwave synthesizer, providing analytically pure material by filtration. Further optimization of time and temperature identified 10 min microwave irradiation at 170 °C as the optimal reaction conditions to deliver **17** in >98% yield on either a 50 mg or 1 g reaction scale.[11] Thus, a 3-step reaction sequence that required >72 h and provided 40–60% yield has been optimized to require only 30 min total reaction time with overall yields in excess of 80%.

As shown in Table 1, the MAOS conditions proved to be general for the reacting malondialdehyde providing

Table 1. Representative pyrazolo[1,5-*a*]pyrimidines **1**

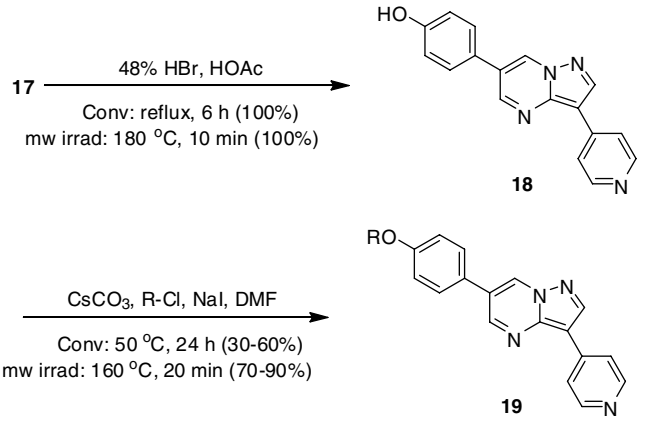


Entry	Ar_1	Ar_2	Yield[a] (%)
1a			99
1b			82
1c			94
1d			95
1e			89
1f			84

[a] Isolated yields for analytically pure material after neutralization and filtration. All give >90% conversion by analytical LCMS.

C-6 functionalized pyrazolo[1,5-*a*]pyrimidines **1** in excellent isolated yields by simple filtration to afford the acetate salts. Neutral products could be obtained by neutralization of the crude reaction with concentrated NH_4OH and filtration.[7] Pyridine heterocycles (entries 1a, 1b, 1d and 1f) were tolerated in the pyrazole component **11**, as were unsubstituted phenyl congeners (entries 1c and 1e). A 5-amino-4-bromopyrazole derivative **11** (where $Ar_1 = Br$) afforded the desired product **1**, but in low yield and was found to rapidly decompose upon standing. This was unfortunate as the bromo analogue offered opportunities for further analogue libraries through MAOS–Suzuki couplings. With respect to the malonoaldehyde component **12**, both aryl and heteroaryl congeners provided uniformly good results. Thus, our new MAOS protocol (10 min, 170 °C) afforded the desired products **1** in >80% yield.

For the initial screening lead **17**, we also hoped to optimize a protocol to elaborate the methyl ether moiety with diverse alkyl chain lengths and functional groups as demonstrated in the literature for KDR kinase inhibitors.[1,2] Once again, we employed MAOS protocols for both the deprotection and the alkylation steps (Scheme 4). Lead **17** was deprotected in the microwave in 10 min at 180 °C to afford quantitative yield of phenol **18**, similar in yield to conventional heating, but with accelerated reaction time.[2] Alkylation of **18** with a diverse collection of functionalized alkyl chlorides delivered analogues **19** in only 20 min in 70–90% yield (as compared to 24 h at reflux and 30–60% yield). With this protocol, we quickly prepared several 24-member libraries of analogues **19**, for which biological data will be disclosed soon.

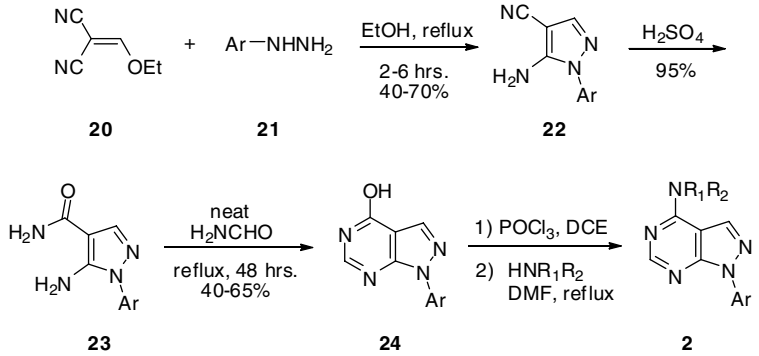


Scheme 4. MAOS synthesis of pyrazolo[1,5-*a*]pyrimidine **16**.

Classical conditions for the synthesis of pyrazolo[3,4-*d*]-pyrimidines **2** involve the treatment of an aryl hydrazine **21** with ethoxymethylenemalonitrile **20** in refluxing ethanol for 2–6 h to provide 4-cyano-5-aminopyrazole **22** in 50–70% yields (Scheme 5).[3,4] Hydrolysis of the nitrile with aqueous H_2SO_4 delivers the corresponding carboxamide **23** which is then heated at reflux for 48 h in neat formamide to provide the 1-aryl pyrazolo[3,4-*d*]-pyrimidin-4-ol **24** in 40–65% yield. Conversion to the chloride with $POCl_3$ and subsequent S_NAr with an amine provides pyrazolo[3,4-*d*]pyrimidine **2** in two operations without isolation of the chloride.[3,4]

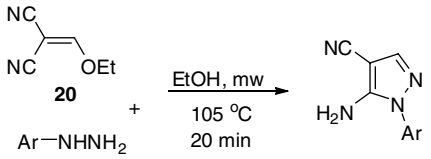
Similar to our work with optimizing the synthesis of **1**, our attention now focused on optimizing the synthesis of the requisite 4-cyano-5-aminopyrazoles **22** employing MAOS. After varying time and temperature, optimal conditions employed a 1:1 ratio of **20**:**21** under microwave irradiation at 105 °C for 20 min to deliver 4-cyano-5-aminopyrazoles **22** (Table 2). In this instance, MAOS had little effect on chemical yields (as pure products were ultimately obtained by recrystallization), but did, once again, shorten the reaction time from 2–6 h to only 20 min. Analogues **22** were smoothly converted into the carboxamide derivative **23** by treatment with concentrated H_2SO_4 at 0 °C for 1 h (yields averaged 95%).

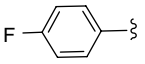
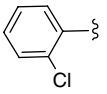
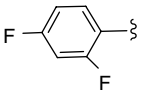
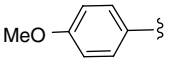
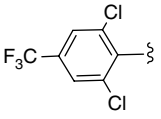
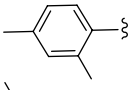
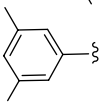
Once analogues **23** were in hand, conventional thermal conditions were quickly adapted and optimized on a single-mode microwave synthesizer. In the event, exposing carboxamide aminopyrazoles **23** in neat formamide to microwave irradiation at 200 °C for 20 min afforded pyrazolo[3,4-*d*]pyrimidines **24** in 48–92% isolated yield (Table 3). Importantly, these conditions afforded equivalent results on either a 50 mg or 1 g reaction scale. Thus, a reaction step that required >48 h at reflux and provided 40–65% yield has been optimized to 20 min with yields generally in excess of 74%.[3,4,12]



Scheme 5. Classical synthesis of pyrazolo[3,4-*d*]pyrimidines **2**.

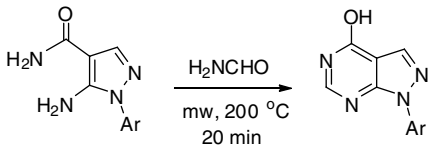
Table 2. Representative 4-cyano-5-aminopyrazoles **22**

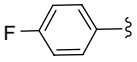
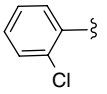
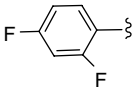
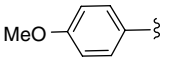
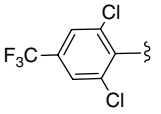
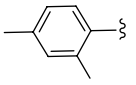
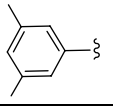


Entry	Ar	Yield[a] (%)
22a		71
22b		42
22c		54
22d		64
22e		70
22f		65
22g		77

[a] Isolated yields for analytically pure material after recrystallization.

Table 3. Representative pyrazolo[3,4-*d*]pyrimidines **24**

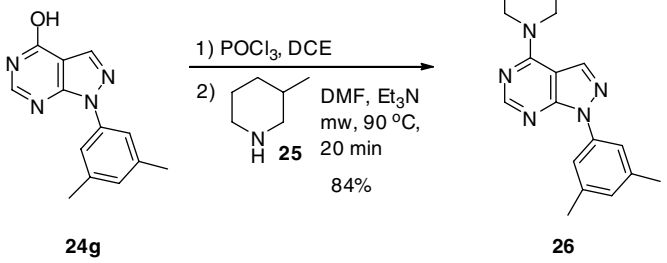


Entry	Ar	Yield[a] (%)
24a		74
24b		92
24c		81
21d		88
24e		77
24f		48
24g		91

[a] Isolated yields for analytically pure material after recrystallization.

Final elaboration into analogues for biological testing involved conversion to the chloride and a subsequent S_NAr reaction with a set of diverse amines to deliver analogues **2**. For example, pyrazolo[3,4-*d*]pyrimidine **24g** was treated with $POCl_3$ in DCE. When conversion to the chloride was judged complete by LCMS, the reaction was concentrated, re-dissolved in DMF and transferred to a 5 mL microwave reaction vessel. 3-Methylpiperidine **25** was added along with Et_3N and the reaction was heated in the microwave at 90 °C for 15 min to afford **26** in 84% isolated yield for the two step sequence (Scheme 6). In a similar fashion, all analogues **24** were converted to their corresponding chloride and subjected to S_NAr reactions with 24 diverse amines to produce 168 analogues of **2** in 52–94% yields (two step library synthesis).[12] Biological data for all final products will soon be disclosed.

In summary, we have applied MAOS to the preparation of pyrazolo[1,5-*a*] and pyrazolo[3,4-*d*]pyrimidines, **1** and **2**, respectively, as well as the aminopyrazole precursors **11** and **19**, respectively. In each case, reaction time and/or yield was dramatically improved under these MAOS protocols. Moreover, these new protocols allow for an iterative analogue library synthesis approach for lead optimization to be employed for the rapid synthesis



Scheme 6. MAOS synthesis of 4-piperidinyl pyrazolo[3,4-*d*]pyrimidine **26**.

of 100 s of analogues of **1** and **2**. Further refinements and biological data for these analogues will be reported in due course.

Acknowledgments

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11. Typical MAOS experimental for pyrazolo[1,5-*a*]pyrimidine **1**, 6-(4-methoxy)-3-(pyridin-4-yl)pyrazolo[1,5-*a*]-pyrimidine. To a 5 mL microwave reaction vessel was placed **13** (565 mg, 5 mmol) in a 3 mL solution of dimethylformamide–dimethlyacetal:DMF:$PhCF_3$ (1:1:2). The vial was heated in a microwave synthesizer to 150 °C for 10 min. LCMS (single peak, 1.1 min, *m*/*e*, 174.1 (M+1)) indicated that all **13** was consumed affording **14**. Hydrazine (160 μL, 5.1 mmol) was then added via syringe and the vial heated to 140 °C for 10 min. Aqueous work-up, followed by preparative LCMS afforded 680 mg (85%) of 4-(pyridin-4-yl)-1*H*-pyrazol-5-amine, **15** as a purple solid. ^{1}H NMR (DMSO-d_6, 400 MHz): δ (ppm): 8.38 (d, $J = 6$ Hz, 2H), 7.84 (s, 1H), 7.47 (d, $J = 6$ Hz, 2H), 5.14 (br s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm) 154, 149.5, 141.4, 132, 124, 119; LCMS, single peak, 0.39 min, *m*/*e*, 161.1 (M+1). Compound **15** (644 mg, 4 mmol) was dissolved in 3.5 mL of 5% AcOH/EtOH and then 2-(4methoxyphenyl)malonaldehyde **16** (712 mg, 4 mmol) was added. The microwave reaction vessel was capped and then heated at 170 °C for 10 min. Upon rapid cooling to 40 °C, the product precipitated from solution NH_4OH was added to neutralize the AcOH, and the product collected by filtration and washed with water to afford 1.18 g of 6-(4-methoxyphenyl)-3-(pyridin-4-yl)pyrazolo[1,5-*a*]pyrimidine, **17**, (98%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 Hz): δ (ppm): 8.87 (d, $J = 2$ Hz, 1H), 8.82 (d, $J = 2$ Hz, 1H), 8.64 (d, $J = 5.6$ Hz, 2H), 8.53 (s, 1H), 8.01 (d, $J = 6$ Hz, 2H), 7.54 (d, $J = 8.8$ Hz, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 3.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm): 160, 150.3, 150.1, 144.4, 143.2, 139.6, 131.6, 128, 125.7, 123.2, 120.2, 115, 107.7, 55.4; LCMS, single peak, 2.27 min, *m*/*e*, 303.1 (M+1).
12. Typical MAOS experimental for pyrazolo[3,4-*d*]pyrimidine, 1-(3,5-dimethylphenyl)-4-(3-methylpiperidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol **26**. 3,5-Dimethylhydrazine hydrochloride was partitioned between 2 M sodium hydroxide solution and dichloromethane. The organic layer was separated, dried and reduced under vacuum to give the free hydrazine (1.90 g, 14 mmol). The free hydrazine and ethoxymethylenemalononitrile (1.70 g, 14 mmol) in ethanol were irradiated at 105 °C for 20 min by microwave. The crude product was recrystallized from ethanol to yield **22g**, 5-amino-1-(3,5-dimethylphenyl)-1*H*-pyrazole-4-carbonitrile, as a yellow solid (2.30 g, 77%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.58 (s, 1H), 7.08 (s, 3H), 4.81 (s, 2H), 2.37 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.87, 140.99, 139.87, 136.62, 130.48, 121.80, 114.25, 75.38, 21.15; LCMS, single peak, 2.73 min, *m*/*e*, 213.1 (M+1). Compound **22g** (4.6 g, 21.7 mmol) was then treated with concentrated H_2SO_4 (30 mL), followed by pouring over ice and neutralized with NH_4OH to provide, after filtration, **23g**, 5-amino-1-(3,5-dimethylphenyl)-1*H*-pyrazole-4-carboxamide as a yellow solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.86 (s, 1H), 7.14 (s, 2H), 6.99 (s, 1H), 6.32 (s, 2H), 2.32 (s, 6H); ^{13}C NMR (DMSO-d_6, 100 MHz): δ (ppm): 166.1, 149.1, 138.7, 138, 128.4, 120.7, 97, 20.8; LCMS, single peak, 2.33 min, *m*/*e*, 231.1 (M+1). A suspension of 5-amino-1-(3,5-dimethylphenyl)-1*H*-pyrazole-4-carboxamide **23g** (2.30 g, 10 mmol) in formamide was irradiated at 200 °C for 20 min by microwave. The cooled solution was diluted with water. The product was filtered, washed with water and dried over in vacuo to afford **24g**, 1-(3,5-dimethylphenyl)-1*H*-pyrazolo[3,4-*d*]pyrimidin-4-ol, as a gray solid (2.18 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.22 (s, 1H), 8.19 (s, 1H), 7.63 (s, 2H), 7.02 (s, 1H), 2.35 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 156.76, 148.14, 138.05, 137.98, 135.22, 128.14, 119.27, 107.21, 20.57; LCMS, single peak, 2.66 min, *m*/*e*, 241.1 (M+1). **24g** (2.18 g, 9.1 mmol) was dissolved in DCE and cooled to 0 °C. $POCl_3$ (1.4 g, 9.3 mmol) added and reaction monitored by LCMS. Reaction washed with water and concentrated to afford pure 4-chloro-1-(3,5-dimethylphenyl)-1*H*-pyrazolo-[3,4-*d*]pyrimidine. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.92 (s, 1H), 8.45 (s, 1H), 7.72 (s, 2H), 7.06 (s, 1H), 2.43 (s, 6H); ^{13}C NMR ($CDCl_3$ 75 MHz) δ 153.5, 152.7, 152, 139.3, 137.3, 134, 129.8, 119.6, 114.8, 21.4; LCMS, single peak, 3.81 min, *m*/*e*, 259.1 (M+1). Then,4-chloro-1-(3,5-dimethylphenyl)-1*nH*-pyrazolo[3,4-*d*]pyrimidine (1.9 g, 7.36 mmol) was dissolved in 5 mL of DMF and 1 mL of Et_3N in a 10 mL microwave reaction vessel, followed by 3-methylpiperidine **25** (1 mL, 11 mmol, 1.5 equiv) The reaction was irradiated with microwaves for 20 min at 200 °C. The final product was purified by mass-directed HPLC to afford **26**, 1-(3,5-dimethylphenyl)-4-(3-methyl-

piperidin-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine, as an off-white solid (1.98 g, 84%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.42 (s, 1H), 8.08 (s, 1H), 7.69 (s, 2H), 6.96 (s, 1H), 4.62 (s, 2H), 3.19 (dd, $J = 11.6$, 12.0 Hz, 1H), 2.84 (dd, $J = 11.6$, 12.0 Hz, 1H), 2.40 (s, 6H), 1.95–1.56 (m, 4H), 1.35–1.23 (m, 1H), 1.02 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 156.79, 155.61, 154.28, 138.75, 138.68, 133.70, 128.46, 120.01, 101.43, 53.05, 46.37, 32.99, 31.19, 25.11, 21.43, 19.05; LCMS, single peak, 3.35 min, *m*/*e*, 322.1 (M+1).