Efficient *N*-Arylation/Dealkylation of Electron Deficient Heteroaryl Chlorides and Bicyclic Tertiary Amines under Microwave Irradiation

Hong-Jun Wang,* Yi Wang, Adam J. Csakai, William G. Earley, and R. Jason Herr

Medicinal Chemistry Department, Albany Molecular Research, Inc (AMRI), PO Box 15098, 26 Corporate Circle, Albany, New York 12212

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A highly efficient procedure was developed for the microwave-assisted synthesis of *N*-heteroaryl-4-(2-chloroethyl)piperazines and *N*-heteroaryl-4-(2-chloroethyl)piperidines. Microwave irradiation of electron deficient heteroaryl chlorides with 1,4-diazabicyclo[2.2.2]octane (DABCO) at 160 °C for 15 min led to *N*-heteroaryl-4-(2-chloroethyl)piperazines in good to excellent yields. In a similar manner, microwave irradiation of electron deficient heteroaryl chlorides with quinuclidine at 180 °C for 15 min provided *N*-heteroaryl-4-(2-chloroethyl)piperidines in good to excellent yields. Extension of the method was demonstrated by the development of a one-pot, two-step microwave-assisted protocol for the synthesis of 4-(2-acetoxyethyl)-substituted *N*-heteroarylpiperazines and *N*-heteroarylpiperidines to demonstrate the production of a small library in a parallel fashion.

Introduction

The *N*-heteroarylpiperazine and *N*-heteroarylpiperidine motifs are important core structures found in many drug substances in use or under investigation today and continue to be useful privileged subunits found frequently in many medicinal chemistry programs (Figure 1).[1] For instance, *N*-heteroaryl-containing piperazine derivatives have been shown to be particularly useful toward a wide range of biological targets, such as modulators of kinases, immunosuppressants, and as potent ligands of serotonin receptor subtypes, just to name a few.[2] Similarly, piperidines bearing an *N*-heteroaryl moiety are known ligands under investigation for the potential treatment of neurological and proliferative diseases, for HIV infection, and for disorders associated with pain.[3]

As part of an ongoing research program, we required a facile route to prepare several small libraries of heteroaryl-substituted piperazines and piperidines, and in particular, we found a need to prepare scaffolds containing a two-carbon tether at the heterocyclic C-4 or N-4 position with a pendant moiety to facilitate later-stage functionalization. While we were evaluating several routes, we became aware of a 1963 communication by Ross and Finkelstein,[4a] in which an *N*-arylation reaction between 4-chloronitrobenzene (**1**) and 1,4-diazabicyclo[2.2.2]octane (DABCO, **2**) was carried out at high temperature, providing a near-quantitative yield of the *N*-arylpiperazine product **4**, containing a pendant quaternary ammonium moiety (Scheme 1). It was postulated that the first intermediate from an intermolecular S_NAr reaction was the *N*-aryl quaternary ammonium salt **3**, which was not isolated but further reacted in situ with a second equivalent of DABCO, resulting in complete conversion to the piperazine **4**. We reinvestigated this reaction utilizing a microwave synthesizer rather than relying on the thermal process and found that we could build upon this idea by introduction of the electron deficient heteroaryl chlorides into this transformation, which allowed the selective *N*-arylation/dealkylation[4] to give **7a** instead of the quaternary ammonium salt **8a**. Thus, we reported our microwave-assisted method reacting DABCO with several heteroaryl chlorides [such as 2-chloropyrimidine (**5a**)] and external nucleophiles to provide *N*-heteroaryl 4-(2-substituted-ethyl)piperazines **9** in good yields for the two-step process.[5]

In our previous study, nitrogen and oxygen nucleophiles were utilized in the second step to generate 2-aminoethyl and 2-alkoxy/aryloxy products **9** (Scheme 1). We did not isolate any intermediate adducts in the reaction sequence but instead carried the reaction mixtures into the second step. In this communication, we now report that the 2-chloroethyl adducts **7** may indeed be isolated as pure adducts, providing a very rapid and convenient method for the construction of 4-(2-chloroethyl) *N*-heteroarylpiperazines **7** from DABCO (**2**, A = N, Scheme 2). These scaffolds **7** (A = N) can be further elaborated in separate transformations, which we report with full details here in the case of preparing 4-(2-

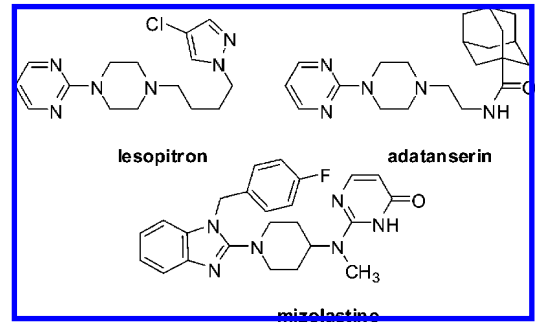

Figure 1. Three *N*-heteroaryl-heterocycle active pharmaceutical ingredients (APIs).

* To whom correspondence should be addressed. E-mail: Hong-Jun.Wang@amriglobal.com.

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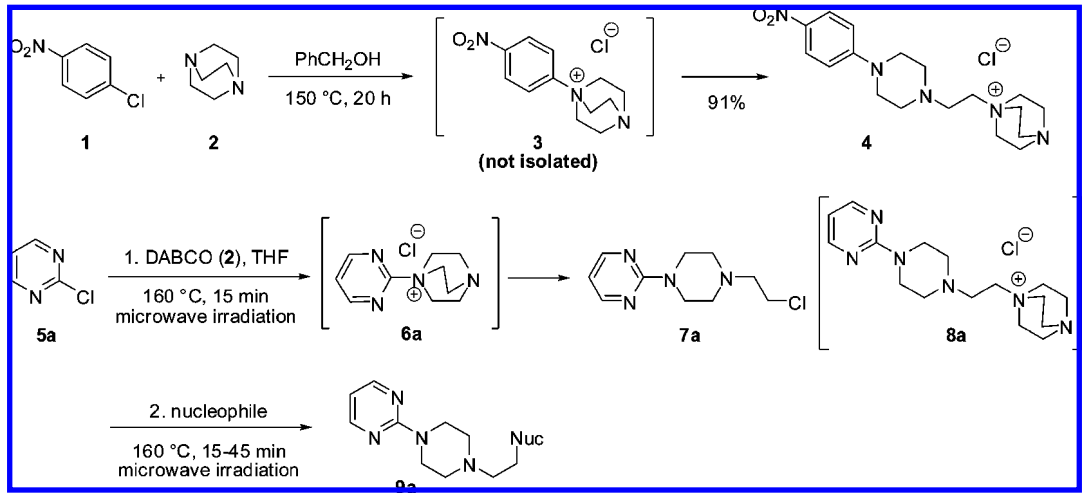
Scheme 1. Tandem *N*-Arylation/Dealkylation of Heteroaryl Chlorides with DABCO



acetoxyethyl) *N*-heteroarylpiperazine adducts **9** (A = N). Also in this communication, we are pleased to report a new extension of the tandem *N*-arylation/dealkylation protocol to another bicyclic tertiary amine quinuclidine (**10**, A = CH) for the synthesis of the novel 4-(2-chloroethyl)piperidine adducts **11** (A = CH), and to describe their conversion to the corresponding 4-(2-acetoxyethyl)piperidines **12** (A = CH).

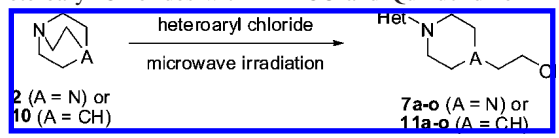
Results and Discussion

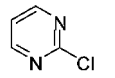
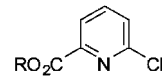
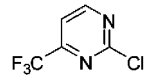
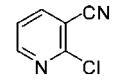
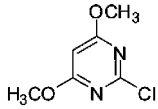
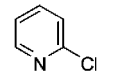
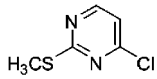
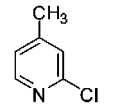
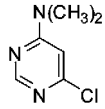
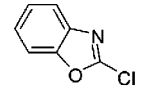
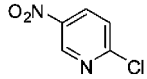
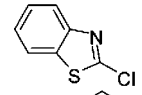
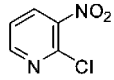
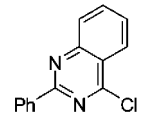
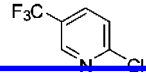
Microwave-assisted organic synthesis (MAOS) has attracted increasing attention because of its potential to speed up drug discovery research.[6] Many organic transformations have been accelerated by the use of microwave irradiation, with reaction times often dramatically reduced from hours to minutes or even seconds. Moreover, there have been reports of microwave-assisted syntheses of combinatorial libraries.[7] In our recent communication, we reported the efficient *N*-arylation/dealkylation of a number of heteroaryl chlorides with DABCO under microwave irradiation, first exploring the reaction with 2-chloropyrimidine under microwave irradiation (0.7 M, 160 °C, 15 min) as shown in Scheme 1. A variety of solvents were investigated in great detail, and we found that the use of THF was optimal in many cases, although reactions also proceeded well in 1,4-dioxane or DME. The microwave reactions in THF were superior in terms of conversion and yield when compared to the corresponding reactions under thermal activation by conventional heating conditions, in which the reactions only minimally proceeded at refluxing temperature.[8]

We were thus delighted to find that subjection of equimolar amounts of DABCO and 2-chloropyrimidine (**2a**) in THF to microwave-assisted heating at 160 °C for only 15 min resulted in the formation of the *N*-heteroarylpiperazine **7a** (A = N) in 87% yield after a simple isolation procedure (Table 1, entry 1). Furthermore, excellent yields were observed for 2-chloropyrimidines bearing either an electron-withdrawing moiety (entry 3) or two electron-donating substituents (entry 5). 4-Chloropyrimidine bearing a 2-methylthio substituent afforded an 81% yield of the adduct **7d** (entry 7), whereas the corresponding C-6-(*N*,*N*-dimethylamino) substrate provided a lower yield (25%) of **7e** (entry 9). Optimizing conditions such as irradiation time, temperature, and DABCO loading did not result in any significant improvement in yield of **7e**, in agreement with a recent study reporting the poor reactivity of this substrate toward a high-temperature *N*-arylation/dealkylation reaction with a benzylpyrrolidine.[4g] The activated regioisomeric substrates 2-chloro-5-nitropyridine and 2-chloro-3-nitropyridine resulted in yields of 92% and 52%, respectively (entries 11 and 13), and 2-chloropyridines bearing other electron-withdrawing substituents also led to good results (entries 15, 17, and 19). It was, however, interesting but not surprising to find that the *N*-arylation/dealkylation products were not observed at all when the unactivated substrates 2-chloropyridine and 2-chloro-4-methylpyridine were used (entries 21 and 23). Nevertheless, the reaction of DABCO with the other heteroaryl chlorides 2-chlorobenzoxazole (entry 25), 2-chlorobenzothiazole (entry 27), and 4-chloro-2-phenylquinazoline (entry 29) all gave satisfactory results.

To further expand the usefulness of our protocol, we were able to work out the *N*-arylation/dealkylation method to include quinuclidine (**10**, A = CH) as an initial nucleophile to react with the same array of heteroaryl chlorides (Table 1). For this precursor, the reactions were carried out in the microwave synthesizer at an internal temperature of 180 °C instead of 160 °C to ensure full conversion after 15 min. Thus, under these reaction conditions, most of the activated heteroaryl substrates proceeded to give good to excellent yields of the corresponding 4-(2-chloroethyl)piperidines **11** (A = CH), except for the unactivated substrates 2-chloropyridine and 2-chloro-4-methylpyridine, which were unreactive toward the transformation. In general, the reaction of heteroaryl chlorides with quinuclidine provided uniformly lower yields than the corresponding reaction with DABCO, with the exception of 4-chloro-6-(*N*,*N*-dimethylamino)pyrimidine, which gave a yield of 45% (entry 10). It should be noted that a competition study of the transformation of 2-chloropyrimidine and quinuclidine to product **11a** under conventional heating conditions was also conducted in THF, with ^{1}H NMR analyses indicating the formation of **11a** at less than 5%.[8]

Table 1. *N*-Arylation/Dealkylation of Heteroaryl Chlorides with DABCO and Quinuclidine



Entry	Heteroaryl Chloride	Product	Isolated Yield	Entry	Heteroaryl Chloride	Product	Isolated Yield
1		**7a** (A = N)	87%[a]	17		**7i** (A = N, R = Et)	83%[a]
2		**11a** (A = CH)	82%[b]	18		**11i** (A = CH, R = CH_3)	58%[b]
3		**7b** (A = N)	91%[a]	19		**7j** (A = N)	79%[a]
4		**11b** (A = CH)	68%[b]	20		**11j** (A = CH)	64%[b]
5		**7c** (A = N)	95%[a]	21		**7k** (A = N)	0[a,c]
6		**11c** (A = CH)	88%[b]	22		**11k** (A = CH)	0[b,c]
7		**7d** (A = N)	81%[a]	23		**7l** (A = N)	0[a,c]
8		**11d** (A = CH)	77%[b]	24		**11l** (A = CH)	0[b,c]
9		**7e** (A = N)	25%[a]	25		**7m** (A = N)	95%[a]
10		**11e** (A = CH)	45%[b]	26		**11m** (A = CH)	76%[b]
11		**7f** (A = N)	92%[a]	27		**7n** (A = N)	89%[a]
12		**11f** (A = CH)	70%[b]	28		**11n** (A = CH)	79%[b]
13		**7g** (A = N)	52%[a]	29		**7o** (A = N)	67%[a]
14		**11g** (A = CH)	47%[b]	30		**11o** (A = CH)	55%[b]
15		**7h** (A = N)	69%[a]				
16		**11h** (A = CH)	60%[b]				

[a] Conditions: DABCO (**2**, A = N), heteroaryl chloride, THF, microwave irradiation, 160 °C, 15 min. [b] Conditions: quinuclidine (**10**, A = CH), heteroaryl chloride, THF, microwave irradiation, 180 °C, 15 min. [c] No reaction products detected.

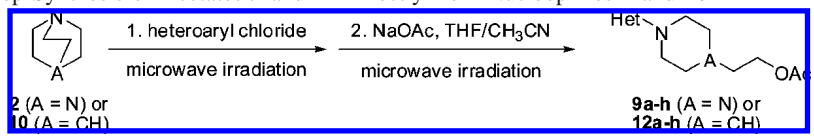
With the aim of developing an efficient parallel protocol for the synthesis of combinatorial libraries, we further examined our one-pot, two-step procedure for the conversion of *N*-heteroaryl-4-(2-chloroethyl)piperazines to the corresponding acetates. As shown in Table 2, the reaction of selected heteroaryl chlorides with DABCO gave *N*-heteroaryl-4-(2-chloroethyl)piperazines, which without purification were treated with 3 equiv of sodium acetate at 160 °C for an additional 15 min to afford the 4-(2-acetoxyethyl) products **9a**−**h** (A = N) in good to excellent yields. While we have previously reported these results in preliminary form,[5] we provide the full experimental details here for the first time.

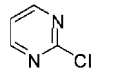
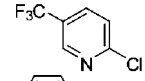
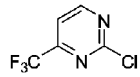
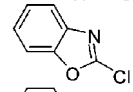
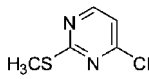
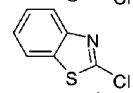
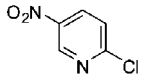
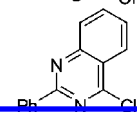
In addition, we were pleased to find that the corresponding protocol applied to the same set of heteroaryl chloride substrates with quinuclidine (**10**, A = CH) generated the requisite *N*-heteroaryl-4-(2-chloroethyl)piperidines **12a**−**h** (A = CH), with this being the first report of this extension. While the isolated yields of products **12** are roughly on par with the yields of piperazine adducts **9**, we did find that the reaction of the 4-(2-chloroethyl)piperidine adducts with sodium acetate proceeded at a slower rate than the piperazine series at 160 °C. To overcome this drop in reaction rate, we identified tetrabutylammonium chloride as an effective phase-transfer catalyst for this transformation. As a result, treatment of the intermediate 4-(2-chloroethyl)piperidine adducts with 5 equiv of sodium acetate and 0.3 equiv of tetrabutylammonium chloride under microwave irradiation at 170 °C for 15 min afforded the acetates **12** (A = CH) in good to excellent yields as reported in Table 2. It is also noteworthy that (in most cases), the substantially pure products **9** and **12** were directly obtained by a simple filtration of the crude reaction mixture through a pad of silica gel or Celite to remove the polar byproducts, followed by removal of the solvents under reduced pressure.

Conclusion

In conclusion, we have developed a highly efficient microwave procedure for the synthesis of *N*-heteroaryl 4-(2-chloroethyl)piperazines **7** and *N*-heteroaryl 4-(2-chloroethyl)piperidines **11**, which are valuable scaffolds for the generation of drug-like small molecule libraries. Under microwave irradiation, the *N*-arylation/dealkylation of electron deficient heteroaryl chlorides with DABCO or quinuclidine leads to the production of *N*-heteroaryl-substituted piperazines and piperidines, respectively, containing a 2-chloroethyl substituent at the heterocyclic C-4 or N-4 position, which can be used as a pendant moiety to facilitate later-

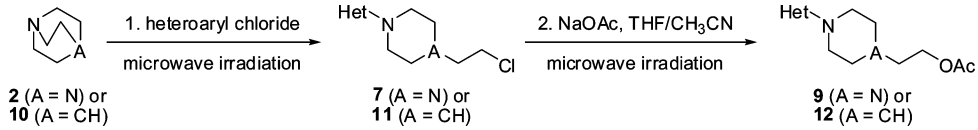
Table 2. One-Pot, Two-Step Synthesis of Acetates **9** and **12** Directly from Nucleophiles **2** and **10**



Entry	Heteroaryl Chloride	Product	Isolated Yield	Entry	Heteroaryl Chloride	Product	Isolated Yield
1		**9a** (A = N)	90%[a]	9		**9e** (A = N)	68%[a]
2		**12a** (A = CH)	92%[b]	10		**12e** (A = CH)	56%[b]
3		**9b** (A = N)	91%[a]	11		**9f** (A = N)	91%[a]
4		**12b** (A = CH)	59%[b]	12		**12f** (A = CH)	85%[b]
5		**9c** (A = N)	85%[a]	13		**9g** (A = N)	78%[a]
6		**12c** (A = CH)	79%[b]	14		**12g** (A = CH)	72%[b]
7		**9d** (A = N)	92%[a]	15		**9h** (A = N)	81%[a]
8		**12d** (A = CH)	77%[b]	16		**12h** (A = CH)	71%[b]

[a] Conditions: Step one, DABCO (**2**, A = N), heteroaryl chloride, THF, microwave irradiation, 160 °C, 15 min; step two, NaOAc, THF, CH_3CN, microwave irradiation, 160 °C, 15 min. [b] Conditions: Step one, quinuclidine (**10**, A = CH), heteroaryl chloride, THF, microwave irradiation, 180 °C, 15 min; step two, NaOAc, Bu_4NCl, THF, CH_3CN, microwave irradiation, 170 °C, 15 min.

Scheme 2. *N*-Arylation/Dealkylation to Provide 4-(2-Chloroethyl) Heterocycles and Further Elaboration



stage functionalization. We also demonstrated that the unisolated chloride adducts may be further converted to the corresponding 4-(2-acetatoxyethyl) products in good to excellent yields by treatment of the reaction products with sodium acetate under a second set of microwave conditions. The efficient microwave-assisted transformation, together with a relatively straightforward purification process, makes this protocol ideal for use when carrying out the parallel synthesis of small molecule libraries.

Experimental Section

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance spectra were obtained on a Bruker AV 300 or a Bruker AV 500 spectrometer at 300 and 500 MHz, respectively. Carbon nuclear magnetic resonance spectra were obtained on a Bruker AV 300 or a Bruker AV 500 spectrometer at 75 and 125 MHz, respectively. Spectra are given in parts per million (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane was used as an internal standard for proton and carbon spectra. Low resolution mass spectra were obtained on a Perkin-Elmer Sciex API-150 MCA atmospheric pressure chemical ionization (APCI), single quadrupole mass spectrometer interfaced to an Agilent HP 1100 HPLC system with a Symmetry C8(2) analytical column. High resolution mass spectra were obtained on a TOF mass spectrometer using electrospray ionization at the Center for Functional Genomics, University at Albany (Albany, NY). The microwave reactions were conducted in a Biotage Initiator or a SmithCreator from Personal Chemistry.

General Procedure for the Synthesis of *N*-Heteroaryl-4-(2-chloroethyl)piperazines 7. A 2−5 mL microwave reactor vial containing a magnetic stir bar was charged with heteroaryl chloride (2.00 mmol), 1,4-diazabicyclo[2.2.2]octane (DABCO, **2**, 231 mg, 2.06 mmol), and tetrahydrofuran (3 mL). The vial was sealed and irradiated in a Biotage Initiator or a SmithCreator to reach 160 °C in 2−3 min, after which the mixture was held at 160 °C for 15 min. After this time, the reaction mixture was diluted with methylene chloride (40 mL), and the resulting mixture was filtered through a pad of silica gel (5 mL) and Celite (5 mL) under reduced pressure, further eluting with ethyl acetate (100 mL). The solvents from the combined organic filtrates were removed under reduced pressure to provide products **7**, the purity of which was determined by ^{1}H NMR analyses or the residues were further purified by flash column chromatography on silica gel.

2-(4-(2-Chloroethyl)piperazin-1-yl)pyrimidine (7a). Yield: white solid (87%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (d, J = 4.8 Hz, 2H), 6.49 (t, J = 4.7 Hz, 1H), 3.85 (t, J = 5.3 Hz, 4H), 3.63 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 7.1 Hz, 2H), 2.58 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6, 157.7, 109.9, 59.9, 53.0, 43.6, 40.9. HRMS (ESI) calcd for $[C_{10}H_{15}ClN_4 + H]^+$: 227.1063; found *m/z* 227.1053.

2-(4-(2-Chloroethyl)piperazin-1-yl)-4-(trifluoromethyl)pyrimidine (7b). Yield: orange solid (91%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.48 (d, J = 4.8 Hz, 1H), 6.75 (d, J = 4.8 Hz, 1H), 3.90 (t, J = 5.0 Hz, 4H), 3.63 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 2.58 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 160.1, 156.3 (q, J = 26.6 Hz),

120.6 (q, J = 275.5 Hz), 104.6 (q, J = 2.0 Hz), 59.8, 52.9, 43.6, 40.9. HRMS (ESI) calcd for $[C_{11}H_{14}ClF_3N_4 + H]^+$: 295.0937; found *m/z* 295.0937.

2-(4-(2-Chloroethyl)piperazin-1-yl)-4,6-dimethoxypyrimidine (7c). Yield: white solid (95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.37 (s, 1H), 3.85 (s, 6H), 3.82 (t, J = 5.1 Hz, 4H), 3.63 (t, J = 7.1 Hz, 2H), 2.77 (t, J = 6.9 Hz, 2H), 2.55 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 160.8, 77.9, 59.9, 53.4, 53.0, 43.7, 40.9. HRMS (ESI) calcd for $[C_{12}H_{19}ClN_4O_2 + H]^+$: 287.1275; found *m/z* 287.1266.

4-(4-(2-Chloroethyl)piperazin-1-yl)-2-(methylthio)pyrimidine (7d). Yield: light yellow oil (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03 (d, J = 6.3 Hz, 1H), 6.18 (d, J = 6.3 Hz, 1H), 3.67 (t, J = 5.1 Hz, 4H), 3.62 (t, J = 6.9 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.58 (t, J = 5.3 Hz, 4H), 2.50 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.4, 161.0, 155.8, 98.4, 59.7, 52.7, 43.6, 40.8, 14.0. HRMS (ESI) calcd for $[C_{11}H_{17}ClN_4S + H]^+$: 273.0941; found *m/z* 273.0937.

6-(4-(2-Chloroethyl)piperazin-1-yl)-*N*,*N*-dimethylpyrimidin-4-amine (7e). Yield: colorless oil (25%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 0.6 Hz, 1H), 5.45 (s, 1H), 3.64−3.57 (m, 6H), 3.06 (s, 6H), 2.77 (t, J = 6.9 Hz, 2H), 2.59 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.2, 162.9, 157.2, 80.6, 59.8, 52.8, 44.1, 40.9, 37.3. MS (APCI): *m/z* 270 $[M + H]^+$.

1-(2-Chloroethyl)-4-(5-nitropyridin-2-yl)piperazine (7f). Yield: brown solid (92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.03 (d, J = 2.7 Hz, 1H), 8.20 (dd, J = 9.6, 2.7 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H), 3.80 (t, J = 5.1 Hz, 4H), 3.63 (t, J = 6.8 Hz, 2H), 2.80 (t, J = 6.8 Hz, 2H), 2.63 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 146.4, 135.1, 133.0, 104.5, 59.6, 52.7, 44.8, 40.8. MS (APCI): *m/z* 271 $[M + H]^+$.

1-(2-Chloroethyl)-4-(3-nitropyridin-2-yl)piperazine (7g). Yield: bright yellow oil (52%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (dd, J = 4.5, 1.5 Hz, 1H), 8.11 (dd, J = 8.1, 1.8, 1H), 6.75 (dd, J = 8.1, 4.5 Hz, 1H), 3.62 (t, J = 6.9 Hz, 2H), 3.49 (t, J = 4.8 Hz, 4H), 2.79 (t, J = 6.9 Hz, 2H), 2.63 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.7, 151.8, 135.6, 133.0, 113.5, 59.7, 52.8, 47.9, 40.8. MS (APCI): *m/z* 271 $[M + H]^+$.

1-(2-Chloroethyl)-4-(5-(trifluoromethyl)pyridin-2-yl)piperazine (7h). Yield: off-white solid (69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.39 (s, 1H), 7.63 (dd, J = 9.0, 2.4 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H), 3.73−3.55 (m, 6H), 2.79 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.3, 145.8 (q, J = 4.4 Hz), 134.5 (q, J = 3.2 Hz), 124.6 (q, J = 270.3 Hz), 115.3 (q, J = 33.1 Hz), 105.6, 59.8, 52.8, 44.6, 40.9. MS (APCI): *m/z* 294 $[M + H]^+$.

Ethyl 6-(4-(2-Chloroethyl)piperazin-1-yl)picolinate (7i). Yield: white solid (83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.80 (d, J = 2.1 Hz, 1H), 8.02 (dd, J = 8.7, 2.1 Hz, 1H), 6.57 (d, J = 9.0 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 3.71 (t, J = 5.1 Hz, 4H), 3.63 (t, J = 6.6 Hz, 2H), 2.78 (t, J = 6.9 Hz, 2H), 2.62 (t, J = 5.1 Hz, 4H), 1.36 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.0, 160.6, 151.0, 138.5, 115.1, 105.1, 60.4, 59.8, 52.8, 44.6, 40.9, 14.4. MS (APCI): *m/z* 298 $[M + H]^+$.

2-(4-(2-Chloroethyl)piperazin-1-yl)nicotinonitrile (7j). Yield: white solid (79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.34 (dd, J = 4.8, 1.8 Hz, 1H), 7.77 (dd, J = 7.5, 2.1 Hz, 1H), 6.75 (dd, J = 7.8, 4.8 Hz, 1H), 3.75 (t, J = 5.1 Hz, 4H), 3.63 (t, J = 6.9 Hz, 2H), 2.80 (t, J = 6.9 Hz, 2H), 2.67 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.5, 151.9, 143.9, 118.1, 114.1, 94.9, 59.7, 53.0, 47.9, 40.8. MS (APCI): *m/z* 251 $[M + H]^+$.

2-(4-(2-Chloroethyl)piperazin-1-yl)benzo[*d*]oxazole (7m). Yield: white solid (95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 6.9 Hz, 1H), 7.17 (td, J = 7.8, 0.9 Hz, 1H), 7.02 (td, J = 7.8, 0.9 Hz, 1H), 3.73 (t, J = 5.1 Hz, 4H), 3.62 (t, J = 6.9 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 2.64 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.5, 149.2, 143.5, 124.4, 121.1, 116.7, 109.1, 60.1, 52.7, 45.9, 41.2. MS (APCI): *m/z* 266 $[M + H]^+$.

2-(4-(2-Chloroethyl)piperazin-1-yl)benzo[*d*]thiazole (7n). Yield: white solid (89%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.60 (dd, J = 7.8, 0.9 Hz, 1H), 7.55 (dd, J = 8.1, 0.6 Hz, 1H), 7.30 (td, J = 7.8, 1.2 Hz, 1H), 7.08 (td, J = 7.8, 0.9 Hz, 1H), 3.67 (t, J = 5.1 Hz, 4H), 3.62 (t, J = 6.9 Hz, 2H), 2.80 (t, J = 6.9 Hz, 2H), 2.66 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.7, 152.7, 130.8, 126.0, 121.5, 120.7, 119.2, 59.7, 52.4, 48.3, 40.8. MS (APCI): *m/z* 282 $[M + H]^+$.

4-(4-(2-Chloroethyl)piperazin-1-yl)-2-phenylquinazoline (7o). Yield: white solid (67%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57−8.53 (m, 2H), 7.96 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.72 (td, J = 6.9, 1.2 Hz, 1H), 7.51−7.38 (m, 4H), 3.90 (t, J = 4.8 Hz, 4H), 3.66 (t, J = 6.9 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H), 2.77 (t, J = 5.1 Hz, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 159.4, 152.9, 138.6, 132.4, 130.2, 129.1, 128.4, 128.3, 124.9, 124.8, 115.4, 59.8, 53.0, 49.7, 40.9. MS (APCI): *m/z* 353 $[M + H]^+$.

General Procedure for the Synthesis of *N*-Heteroaryl-4-(2-chloroethyl)piperidines 11. A 0.5−2 mL microwave reactor vial containing a magnetic stir bar was charged with heteroaryl chloride (0.50 mmol), quinuclidine (**10**, 58 mg, 0.52 mmol), and tetrahydrofuran (0.75 mL). The vial was sealed and irradiated in a Biotage Initiator to reach 180 °C in 2−3 min, after which the mixture was held at 180 °C for 15 min. After this time, the reaction mixture was diluted with methylene chloride (40 mL), and the resulting mixture was filtered through a pad of silica gel (5 mL) and Celite (5 mL) under reduced pressure, further eluting with ethyl acetate (100 mL). The solvents from the combined organic filtrates were removed under reduced pressure to afford products **11**, the purity of which was determined by ^{1}H NMR analyses or the residues were further purified by flash column chromatography on silica gel.

2-(4-(2-Chloroethyl)piperidin-1-yl)pyrimidine (11a). Yield: white solid (82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.28 (d, J = 5.0 Hz, 2H), 6.43 (t, J = 5.0 Hz, 1H), 4.75 (dt, J = 13.5, 2.5 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 2.88 (td, J = 13.5, 3.0 Hz, 2H), 1.85−1.71 (m, 5H), 1.23−1.18 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6, 157.7, 109.3, 43.9, 42.5, 39.1, 33.5, 31.5. HRMS (ESI) calcd for $[C_{11}H_{16}ClN_3 + H]^+$: 226.1111; found *m/z* 226.1127.

2-(4-(2-Chloroethyl)piperidin-1-yl)-4-(trifluoromethyl)pyrimidine (11b). Yield: colorless oil (68%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, J = 4.8 Hz, 1H), 6.70 (d, J = 4.8 Hz, 1H), 4.84−4.78 (m, 2H), 3.64−3.58 (m, 2H), 2.96−2.87 (m, 2H), 1.88−1.72 (m, 5H), 1.25−1.13 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.4, 160.0, 156.3 (q, J = 35.4 Hz), 120.7 (q, J = 275.0 Hz), 104.0 (q, J = 2.6 Hz), 43.9, 42.4, 39.0, 33.4, 31.5. HRMS (ESI) calcd for $[C_{12}H_{15}ClF_3N_3 + H]^+$: 294.0985; found *m*/*z* 294.0975.

2-(4-(2-Chloroethyl)piperidin-1-yl)-4,6-dimethoxypyrimidine (11c). Yield: colorless oil (88%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.34 (s, 1H), 4.75 (d, J = 13.2 Hz, 2H), 3.85 (s, 6H), 3.61 (t, J = 6.6 Hz, 2H), 2.83 (t, J = 12.9 Hz, 2H), 1.90−1.60 (m, 5H), 1.30−1.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 160.8, 77.3, 53.4, 44.0, 42.5, 39.2, 33.6, 31.6. HRMS (ESI) calcd for $[C_{13}H_{20}ClN_3O_2 + H]^+$: 286.1322; found *m*/*z* 286.1332.

4-(4-(2-Chloroethyl)piperidin-1-yl)-2-(methylthio)pyrimidine (11d). Yield: colorless oil (77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 6.3, 1H), 6.18 (d, J = 6.0 Hz, 1H), 4.41 (d, J = 11.4 Hz, 2H), 3.60 (t, J = 6.6 Hz, 2H), 2.88 (td, J = 12.9, 2.4 Hz, 2H), 2.49 (s, 3H), 1.90−1.71 (m, 5H), 1.25−1.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.3, 160.7, 155.7, 98.4, 44.0, 42.3, 38.8, 33.3, 31.2, 14.0. HRMS (ESI) calcd for $[C_{12}H_{18}ClN_3S + H]^+$: 272.0988; found *m*/*z* 272.0983.

6-(4-(2-Chloroethyl)piperidin-1-yl)-*N*,*N*-dimethylpyrimidin-4-amine (11e). Yield: white solid (45%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, J = 0.6 Hz, 1H), 5.46 (s, 1H), 4.40−4.25 (m, 2H), 3.60 (t, J = 6.6 Hz, 2H), 3.06 (s, 6H), 2.90−2.75 (m, 2H), 1.90−1.65 (m, 5H), 1.30−1.10 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.3, 162.7, 157.3, 80.4, 44.5, 42.4, 39.0, 37.4, 33.4, 31.2. MS (APCI): *m*/*z* 269 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)-5-nitropyridine (11f). Yield: yellow solid (70%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, J = 2.1 Hz, 1H), 8.17 (dd, J = 9.6, 2.4 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H), 4.55 (d, J = 12.6 Hz, 2H), 3.61 (t, J = 6.5 Hz, 2H), 3.02 (t, J = 12.6 Hz, 2H), 1.92−1.73 (m, 5H), 1.29−1.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 146.7, 134.6, 133.0, 104.5, 45.3, 42.2, 38.7, 33.2, 31.4. MS (APCI): *m*/*z* 270 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)-3-nitropyridine (11g). Yield: brown gum (47%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (dd, J = 4.5, 1.8 Hz, 1H), 8.11 (dd, J = 8.1, 1.8 Hz, 1H), 6.71 (dd, J = 7.8, 4.5 Hz, 1H), 3.84 (dt, J = 13.5, 2.1 Hz, 2H), 3.61 (t, J = 6.6 Hz, 2H), 3.07−2.98 (m, 2H), 1.95−1.74 (m, 5H), 1.41−1.28 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.0, 151.7, 135.6, 132.8, 112.9, 48.4, 42.3, 38.9, 33.0, 31.4. MS (APCI): *m*/*z* 270 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)-5-(trifluoromethyl)pyridine (11h). Yield: white solid (60%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38−8.37 (m, 1H), 7.59 (dd, J = 9.0, 2.4 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H), 4.40 (dt, J = 13.5, 2.4 Hz, 2H), 3.61 (t, J = 6.6, 2H), 2.91 (td, J = 13.2, 2.4 Hz, 2H), 1.86−1.71 (m, 5H), 1.28−1.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.2, 145.8 (q, J = 4.4 Hz), 134.4 (q, J = 3.2 Hz), 124.7 (q, J = 270.2 Hz), 114.5 (q, J = 32.9 Hz),105.5, 45.1, 42.3, 38.9, 33.3, 31.3. MS (APCI): *m*/*z* 293 [M + H]$^+$.

Methyl 6-(4-(2-Chloroethyl)piperidin-1-yl)picolinate (11i). Yield: white solid (58%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.78 (d, J = 1.8 Hz, 1H), 7.99 (dd, J = 9.0, 2.4 Hz, 1H), 6.59 (d, J = 9.3 Hz, 1H), 4.47 (d, J = 13.2 Hz, 2H), 3.86 (s, 3H), 3.61 (t, J = 6.6 Hz, 2H), 2.93 (t, J = 12.9 Hz, 2H), 1.95−1.65 (m, 5H), 1.28−1.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 160.9, 151.6, 138.8, 114.5, 105.5, 52.0, 45.4, 42.7, 39.3, 33.7, 31.7. MS (APCI): *m*/*z* 283 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)nicotinonitrile (11j). Yield: colorless oil (64%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.32 (dd, J = 4.8, 2.1 Hz, 1H), 7.75 (dd, J = 4.5, 2.1 Hz, 1H), 6.71 (dd, J = 7.5, 4.8 Hz, 1H), 4.39 (td, J = 13.2, 2.1 Hz, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.01 (td, J = 13.2, 2.1 Hz, 2H), 1.86−1.74 (m, 5H), 1.43−1.30 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.9, 151.9, 143.8, 118.3, 113.6, 94.7, 48.5, 42.4, 39.0, 33.2, 31.7. MS (APCI): *m*/*z* 250 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)benzo[*d*]oxazole (11m). Yield: white solid (76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, J = 8.1 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.15 (td, J = 7.7, 0.9 Hz, 1H), 7.00 (td, J = 7.7, 0.9 Hz, 1H), 4.35−4.30 (m, 2H), 3.62 (t, J = 6.6 Hz, 2H), 3.09 (td, J = 12.9, 2.4 Hz, 2H), 1.85−1.73 (m, 5H), 1.37−1.29 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.3, 148.7, 143.3, 123.9, 120.5, 116.1, 108.6, 45.9, 42.2, 38.8, 32.8, 31.0. MS (APCI): *m*/*z* 265 [M + H]$^+$.

2-(4-(2-Chloroethyl)piperidin-1-yl)benzo[*d*]thiazole (11n). Yield: white solid (79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (dd, J = 7.8, 0.9 Hz, 1H), 7.54 (dd, J = 8.1, 0.6 Hz, 1H), 7.31−7.25 (m, 1H), 7.06 (td, J = 7.8, 1.2 Hz, 1H), 4.16 (dt, J = 12.9, 2.1 Hz, 2H), 3.61 (t, J = 6.6 Hz, 2H), 3.14 (td, J = 13.2, 2.4 Hz, 2H), 1.90−1.73 (m, 5H), 1.42−1.25 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 152.9, 130.8, 125.9, 121.2, 120.6, 118.9, 48.8, 42.2, 38.8, 33.0, 31.0. MS (APCI): *m*/*z* 281 [M + H]$^+$.

4-(4-(2-Chloroethyl)piperidin-1-yl)-2-phenylquinazoline (11o). Yield: white solid (55%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57−8.56 (m, 2H), 7.97 (br s, 1H), 7.89−7.87 (m, 1H), 7.73−7.70 (m, 1H), 7.51−7.46 (m, 3H), 7.42−7.39 (m, 1H), 4.49 (d, J = 12.5 Hz, 2H), 3.65 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 12.0 Hz, 2H), 1.96−1.90 (m, 3H), 1.83 (dd, J = 13.5, 6.5 Hz, 2H), 1.56−1.48 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 159.5, 152.8, 138.8, 132.2, 130.1, 129.0, 128.4, 128.3, 125.0, 124.7, 115.5, 50.1, 42.4, 39.0, 33.6, 31.8. MS (APCI): *m*/*z* 352 [M + H]$^+$.

General Procedure for the One-Pot, Two-Step Synthesis of *N*-Heteroaryl-4-(2-acetoxyethyl)piperazines 9. A 2−5 mL microwave reactor vial containing a magnetic stir bar was charged with heteroaryl chloride (2.00 mmol), DABCO (**2**, 231 mg, 2.06 mmol), and tetrahydrofuran (3 mL). The vial was sealed and irradiated in a Biotage Initiator or a SmithCreator to reach 160 °C in 2−3 min, after which the mixture was held at 160 °C for 15 min. The reaction vial was cooled to room temperature and unsealed, and half of the reaction mixture was removed from the vial for analysis. To the remaining half of the reaction mixture was added sodium acetate (246 mg, 3.00 mmol) and acetonitrile (1.5

mL). The reaction vial was again sealed and irradiated to reach 160 °C in 1−2 min, after which the mixture was held at 160 °C for an additional 15 min. After this time, the reaction mixture was diluted with methylene chloride (40 mL), and the resulting mixture was filtered through a pad of silica gel (5 mL) and Celite (5 mL) under reduced pressure. The pad was further eluted with ethyl acetate (100 mL), and the solvents from the combined organic filtrates were removed under reduced pressure to afford products **9**, the purity of which was determined by ^{1}H NMR analyses or the residues were further purified by flash column chromatography on silica gel.

2-(4-(Pyrimidin-2-yl)piperazin-1-yl)ethyl Acetate (9a). Yield: colorless oil (90%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.31 (d, J = 4.7 Hz, 2H), 6.59 (t, J = 4.8 Hz, 1H), 4.24 (t, J = 5.7 Hz, 2H), 3.81 (t, J = 5.1 Hz, 4H), 2.69 (t, J = 5.7 Hz, 2H), 2.58 (t, J = 5.1 Hz, 4H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 162.9, 159.1, 111.3, 62.5, 57.8, 54.3, 44.6, 20.9. HRMS (ESI) calcd for $[C_{12}H_{18}N_4O_2 + H]^+$: 251.1508; found *m*/*z* 251.1509.

2-(4-(4-(Trifluoromethyl)pyrimidin-2-yl)piperazin-1-yl)-ethyl Acetate (9b). Yield: brown oil (91%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.57 (d, J = 4.9 Hz, 1H), 6.87 (d, J = 4.9 Hz, 1H), 4.25 (t, J = 5.7 Hz, 2H), 3.88 (t, J = 5.2 Hz, 4H), 2.70 (t, J = 5.8 Hz, 2H), 2.60 (t, J = 5.2 Hz, 4H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 161.4, 160.1, 156.3 (q, J = 35.3 Hz), 120.6 (q, J = 273.5 Hz), 104.5 (q, J = 2.7 Hz), 61.8, 56.7, 53.2, 43.6, 21.0. HRMS (ESI) calcd for $[C_{13}H_{17}F_3N_4O_2 + H]^+$: 319.1382; found *m*/*z* 319.1394.

2-(4-(2-(Methylthio)pyrimidin-4-yl)piperazin-1-yl)ethyl Acetate (9c). Yield: colorless oil (85%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.91 (d, J = 6.3 Hz, 1H), 6.42 (d, J = 6.3 Hz, 1H), 4.24 (t, J = 5.7 Hz, 2H), 3.72 (t, J = 5.1 Hz, 4H), 2.70 (t, J = 5.7 Hz, 2H), 2.62 (t, J = 5.4 Hz, 4H), 2.47 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 172.4, 162.5, 156.1, 99.6, 62.5, 57.7, 54.0, 44.6, 20.8, 13.9. MS (APCI): *m*/*z* 297 $[M + H]^+$.

2-(4-(5-Nitropyridin-2-yl)piperazin-1-yl)ethyl Acetate (9d). Yield: orange solid (92%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.96 (d, J = 1.8 Hz, 1H), 8.22 (dd, J = 9.5, 2.8 Hz, 1H), 6.82 (d, J = 9.6 Hz, 1H), 4.25 (t, J = 5.7 Hz, 2H), 3.81 (t, J = 5.2 Hz, 4H), 2.70 (t, J = 5.7 Hz, 2H), 2.63 (t, J = 5.2 Hz, 4H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 162.0, 147.1, 136.4, 134.0, 106.4, 62.5, 57.7, 54.1, 45.7, 20.9. MS (APCI): *m*/*z* 295 $[M + H]^+$.

2-(4-(5-(Trifluoromethyl)pyridin-2-yl)piperazin-1-yl)ethyl Acetate (9e). Yield: purple solid (68%). ^{1}H NMR (300 MHz, CD_3OD): δ 8.33 (dd, J = 1.4, 0.8 Hz, 1H), 7.71 (dd, J = 9.0, 2.4 Hz, 1H), 6.87 (d, J = 9.1 Hz, 1H), 4.25 (t, J = 5.7 Hz, 2H), 3.68 (t, J = 5.2 Hz, 4H), 2.70 (t, J = 5.7 Hz, 2H), 2.63 (t, J = 5.1 Hz, 4H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 162.0, 146.4 (q, J = 4.5 Hz), 135.7 (q, J = 3.1 Hz), 126.2 (q, J = 269.2 Hz), 116.2 (q, J = 33.1 Hz), 107.5, 62.5, 57.8, 54.1, 45.5, 20.9. MS (APCI): *m*/*z* 318 $[M + H]^+$.

2-(4-(Benzo[*d*]oxazol-2-yl)piperazin-1-yl)ethyl Acetate (9f). Yield: colorless oil (91%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.33−7.27 (m, 2H), 7.17 (td, J = 7.8, 1.2 Hz, 1H), 7.05 (td, J = 7.8, 1.2 Hz, 1H), 4.24 (t, J = 5.7 Hz, 2H), 3.69 (t, J = 5.1 Hz, 4H), 2.71 (t, J = 5.7 Hz, 2H), 2.67 (t, J = 5.1 Hz, 4H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 163.6, 149.9, 143.5, 125.4, 122.3, 116.8, 110.0, 62.5, 57.7, 53.6, 46.5, 20.9. MS (APCI): *m*/*z* 290 $[M + H]^+$.

2-(4-(Benzo[*d*]thiazol-2-yl)piperazin-1-yl)ethyl Acetate (9g). Yield: white solid (78%). ^{1}H NMR (300 MHz, CD_3OD): δ 7.65 (d, J = 7.8 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.29 (td, J = 8.1, 0.9 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 4.24 (t, J = 5.7 Hz, 2H), 3.63 (t, J = 5.1 Hz, 4H), 2.73−2.66 (m, 6H), 2.06 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD): δ 172.8, 170.7, 153.5, 131.6, 127.2, 122.9, 122.0, 119.7, 62.6, 57.7, 53.6, 49.3, 20.9. MS (APCI): *m*/*z* 306 $[M + H]^+$.

2-(4-(2-Phenylquinazolin-4-yl)piperazin-1-yl)ethyl Acetate (9h). Yield: white solid (81%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57−8.54 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.7 Hz, 1H), 7.51−7.46 (m, 3H), 7.40 (t, J = 7.7 Hz, 1H), 4.26 (t, J = 5.7 Hz, 2H), 3.89 (t, J = 4.7 Hz, 4H), 2.77−2.71 (m, 6H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.0, 164.8, 159.4, 152.9, 138.7, 132.3, 130.1, 129.1, 128.4, 128.3, 124.8 (2C), 115.4, 61.7, 56.8, 53.3, 49.7, 21.1. MS (APCI): *m*/*z* 377 $[M + H]^+$.

General Procedure for the One-Pot, Two-Step Synthesis of *N*-Heteroaryl-4-(2-acetoxyethyl)piperidines 12. A 0.5−2 mL microwave reactor vial containing a magnetic stir bar was charged with heteroaryl chloride (0.50 mmol), quinuclidine (**10**, 58 mg, 0.52 mmol) and tetrahydrofuran (0.75 mL). The vial was sealed and irradiated in a Biotage Initiator to reach 180 °C in 2−3 min, after which the mixture was held at 180 °C for 15 min. The reaction vial was cooled to room temperature and unsealed. To the reaction mixture was added sodium acetate (205 mg, 2.50 mmol), tetrabutylammonium chloride (42 mg, 0.15 mmol), and acetonitrile (0.75 mL). The reaction vial was again sealed and irradiated to reach 170 °C in 1−2 min, after which the mixture was held at 170 °C for an additional 15 min. After this time, the reaction mixture was diluted with methylene chloride (40 mL), and the resulting mixture was filtered through a pad of silica gel (5 mL) and Celite (5 mL) under reduced pressure, further eluting with ethyl acetate (100 mL). The solvents from the combined organic filtrates were removed under reduced pressure to afford products **12**, the purity of which was determined by ^{1}H NMR analyses or the residues were further purified by flash column chromatography on silica gel.

2-(1-(Pyrimidin-2-yl)piperidin-4-yl)ethyl Acetate (12a). Yield: light brown oil (92%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (d, J = 4.8 Hz, 2H), 6.44 (t, J = 4.8 Hz, 1H), 4.74 (dt, J = 13.5, 2.1 Hz, 2H), 4.14 (t, J = 6.6 Hz, 2H), 2.87 (td, J = 13.2, 2.4 Hz, 2H), 2.06 (s, 3H), 1.85−1.72 (m, 2H), 1.72−1.57 (m, 3H), 1.28−1.14 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 161.6, 157.7, 109.3, 62.3, 44.0, 35.2, 33.3, 31.9, 21.0. HRMS (ESI) calcd for $[C_{13}H_{19}N_3O_2 + H]^+$: 250.1556; found *m*/*z* 250.1563.

2-(1-(4-(Trifluoromethyl)pyrimidin-2-yl)piperidin-4-yl-)ethyl Acetate (12b). Yield: colorless gum (59%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (d, J = 4.8 Hz, 1H), 6.70 (d, J = 4.8 Hz, 1H), 4.79 (d, J = 13.2 Hz, 2H), 4.15 (t, J = 6.6 Hz, 2H), 2.90 (td, J = 12.9, 2.4 Hz, 2H), 2.06 (s, 3H), 1.81 (d, J = 14.1 Hz, 2H), 1.75−1.58 (m, 3H), 1.30−1.12 (m,

2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 161.4, 160.0, 156.3 (q, J = 35.4 Hz), 120.6 (q, J = 274.7 Hz), 104.0 (q, J = 1.9 Hz), 62.2, 44.0, 35.2, 33.2, 31.9, 21.0. HRMS (ESI) calcd for $[C_{14}H_{18}F_3N_3O_2 + H]^+$: 318.1429; found m/z 318.1442.

2-(1-(2-(Methylthio)pyrimidin-4-yl)piperidin-4-yl)ethyl Acetate (12c). Yield: colorless oil (79%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (d, J = 6.0 Hz, 1H), 6.18 (d, J = 6.3 Hz, 1H), 4.39 (d, J = 12.0 Hz, 2H), 4.14 (t, J = 6.5 Hz, 2H), 2.86 (td, J = 12.9, 2.4 Hz, 2H), 2.49 (s, 3H), 2.06 (s, 3H), 1.80 (d, J = 13.5 Hz, 2H), 1.77−1.57 (m, 3H), 1.27−1.18 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 171.1, 160.8, 155.6, 98.4, 62.1, 44.1, 35.1, 33.1, 31.6, 21.0, 14.0. MS (APCI): m/z 296 $[M + H]^+$.

2-(1-(5-Nitropyridin-2-yl)piperidin-4-yl)ethyl Acetate (12d). Yield: yellow solid (77%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.02 (d, J = 2.7 Hz, 1H), 8.17 (dd, J = 9.6, 3.0 Hz, 1H), 6.57 (d, J = 9.6 Hz, 1H), 4.53 (d, J = 13.2 Hz, 2H), 4.15 (t, J = 6.6 Hz, 2H), 3.01 (td, J = 13.2, 2.4 Hz, 2H), 2.07 (s, 3H), 1.93−1.81 (m, 2H), 1.81−1.68 (m, 1H), 1.68−1.58 (m, 2H), 1.33−1.16 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 160.2, 146.7, 134.5, 133.0, 104.4, 62.0, 45.4, 35.0, 33.1, 31.8, 21.0. MS (APCI): m/z 294 $[M + H]^+$.

2-(1-(5-(Trifluoromethyl)pyridin-2-yl)piperidin-4-yl)ethyl Acetate (12e). Yield: colorless oil (56%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.40−8.35 (m, 1H), 7.59 (dd, J = 9.0, 2.4 Hz, 1H), 6.63 (d, J = 9.0 Hz, 1H), 4.43−4.37 (m, 2H), 4.14 (t, J = 6.6 Hz, 2H), 2.90 (td, J = 14.1, 2.4 Hz, 2H), 2.06 (s, 3H), 1.83−1.81 (m, 2H), 1.73−1.57 (m, 3H), 1.31−1.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 160.2, 145.8 (q, J = 4.1 Hz), 134.3 (q, J = 3.0 Hz), 124.7 (q, J = 268.3 Hz), 114.4 (q, J = 32.7 Hz), 105.5, 62.1, 45.1, 35.1, 33.1, 31.6, 21.0. MS (APCI): m/z 317 $[M + H]^+$.

2-(1-(Benzo[*d*]oxazol-2-yl)piperidin-4-yl)ethyl Acetate (12f). Yield: white solid (85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35−7.34 (m, 1H), 7.27−7.23 (m, 1H), 7.17−7.15 (m, 1H), 7.02−7.00 (m, 1H), 4.31 (d, J = 13.0 Hz, 2H), 4.16−4.13 (m, 2H), 3.07 (t, J = 12.5 Hz, 2H), 2.06 (s, 3H), 1.83 (d, J = 12.5 Hz, 2H), 1.64−1.63 (m, 3H), 1.35−1.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 161.4, 147.8, 142.3, 122.9, 119.5, 115.2, 107.7, 61.0, 45.0, 34.1, 31.7, 30.5, 20.1. MS (APCI): m/z 289 $[M + H]^+$.

2-(1-(Benzo[*d*]thiazol-2-yl)piperidin-4-yl)ethyl Acetate (12g). Yield: white solid (72%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J = 7.8 Hz, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.28 (t, J = 7.8 Hz, 1H), 7.06 (t, J = 7.8 Hz, 1H), 4.15 (t, J = 6.3 Hz, 4H), 3.12 (td, J = 12.8, 2.4 Hz, 2H), 2.07 (s, 3H), 1.84 (d, J = 12.9 Hz, 2H), 1.69−1.60 (m, 3H), 1.43−1.31 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 168.7, 152.9, 130.8, 125.9, 121.2, 120.6, 118.9, 62.0, 48.9, 35.0, 32.9, 31.5, 21.0. MS (APCI): m/z 305 $[M + H]^+$.

2-(1-(2-Phenylquinazolin-4-yl)piperidin-4-yl)ethyl Acetate (12h). Yield: white solid (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57−8.53 (m, 2H), 7.96 (dd, J = 8.4, 0.6 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H), 7.71 (ddd, J = 8.4, 6.9, 1.5 Hz, 1H), 7.52−7.45 (m, 3H), 7.40 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 4.47 (d, J = 13.2 Hz, 2H), 4.19 (t, J = 6.6 Hz, 2H), 3.23−3.14 (m, 2H), 2.08 (s, 3H), 1.95−1.86 (m, 2H), 1.86−1.60 (m, 3H), 1.60−1.47 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 165.1, 159.5, 152.8, 138.8, 132.2, 130.1, 128.9, 128.4, 128.3, 125.0, 124.7, 115.6, 62.2, 50.2, 35.2, 33.4, 32.2, 21.1. MS (APCI): m/z 376 $[M + H]^+$.

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Supporting Information Available. ^{1}H NMR and ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) For examples, see:(a) Yoshizawa, T.; Ohmoto, K.; Ogawa, K. PCT Int. Pat. Publ. WO 2005118543, 2005. (b) Fiorino, F.; Perissutti, E.; Severino, B.; Santagada, V.; Cirillo, D.; Terracciano, S.; Massarelli, P.; Bruni, G.; Collavoli, E.; Renner, C.; Caliendo, G. *J. Med. Chem.* **2005**, *48*, 5495. (c) Kling, A.; Lange, U. E. W.; Mack, H.; Bakker, M. H. M.; Drescher, K. U.; Hornberger, W.; Hutchins, C. W.; Moeller, A.; Mueller, R.; Schmidt, M.; Unger, L.; Wicke, K.; Schellhaas, K.; Steiner, G. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5567. (d) Waer, M. J. A.; Herdewijn, P. A. M. M.; De Jonghe, S. C. A.; Marchand, A. D. M.; Gao, L.-J. PCT Int. Pat. Publ. WO 2005039587, 2005. (e) Farre, A.; Frigola, J. *Drugs Future* **1994**, *19*, 651. (f) Abou-Gharbia, M. A.; Childers, W. E., Jr.; Fletcher, H.; McGaughey, G.; Patel, U.; Webb, M. B.; Yardley, J.; Andree, T.; Boast, C.; Kucharik, R. J., Jr.; Marquis, K.; Morris, H.; Scerni, R.; Moyer, J. A. *J. Med. Chem.* **1999**, *42*, 5077.

(3) For examples, see:(a) Caldwell, J. J.; Davies, T. G.; Donald, A.; McHardy, T.; Rowlands, M. G.; Aherne, G. W.; Hunter, L. K.; Taylor, K.; Ruddle, R.; Raynaud, F. I.; Verdonk, M.; Workman, P.; Garrett, M. D.; Collins, I. *J. Med. Chem.* **2008**, *51*, 2147. (b) Bruton, G.; Johnstone, V.; Orlek, B. S. PCT Int. Pat. Publ. WO 2006029906, 2006. (c) Murphy, M. A.; Schullek, J. R.; Ward, J. S.; Look, G. C.; Jain, R.; Lee, L. PCT Int. Pat. Publ. WO 2005120503, 2005. (d) Bakthavatchalam, R.; Blum, C. A.; Chenard, B. L.; Zheng, X. PCT Int. Pat. Publ. WO 2006065872, 2006. (e) Mealy, N.; Ngo, J.; Castaner, J. *Drugs Future* **1996**, *21*, 799.

(4) (a) Ross, S. D.; Finkelstein, M. *J. Am. Chem. Soc.* **1963**, *85*, 2603. See also (b) Matsumoto, K.; Hashimoto, S.; Otani, S. *J. Chem. Soc., Chem. Commun.* **1991**, 306. (c) Yoshida, K.; Taguchi, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 919. (d) Axelsson, O.; Peters, D. *J. Heterocyclic Chem.* **1997**, *34*, 461. (e) Ramakrishna, T. V. V.; Elias, A. J.; Vij, A. *Inorg. Chem.* **1999**, *38*, 3022. (f) Khalaf, A. I.; Alvarez, R. G.; Suckling, C. J.; Waigh, R. D. *Tetrahedron* **2000**, *56*, 8567. (g) Hamilton, G. L.; Backes, B. J. *Tetrahedron Lett.* **2006**, *47*, 2229. (h) Reddy, N. D.; Elias, A. J.; Vij, A. *J. Chem. Soc., Dalton Trans.* **1999**, 1515.

(5) Wang, H.-J.; Earley, W. G.; Lewis, R. M.; Srivastava, R. R.; Zych, A. J.; Jenkins, D. M.; Fairfax, D. J. *Tetrahedron Lett.* **2007**, *48*, 3043.

(6) For recent reviews, see:(a) Perreux, L.; Loupy, A. *Tetrahedron* **2001**, *57*, 9199. (b) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225. (c) Lew, A.; Krutzik, P. O.; Hart, M. E.; Chamberlin, A. R. *J. Comb. Chem.* **2002**, *4*, 95. (d) Larhed, M.; Moberg, C.; Hallberg, A. *Acc. Chem. Res.* **2002**, *35*, 717. (e) Mavandadi, F.; Pilotti, A. *Drug Discovery Today* **2006**, *11*, 165.

(7) For examples, see:(a) Murray, J. K.; Gellman, S. H. *J. Comb. Chem.* **2006**, *8*, 58. (b) Werner, S.; Iyer, P. S.; Fodor, M. D.; Coleman, C. M.; Twining, L. A.; Mitasev, B.; Brummond, K. M. *J. Comb. Chem.* **2006**, *8*, 368. (c) Soh, C. H.; Chui, W. K.; Lam, Y. *J. Comb. Chem.* **2006**, *8*, 464. (d) Bianchi, I.; Forlani, R.; Minetto, G.; Peretto, I.; Regalia, N.; Taddei, M.; Ravelia, L. F. *J. Comb. Chem.* **2006**, *8*, 491.

(8) The quaternary ammonium salt was found to be the major component when the reaction was conducted at reflux in THF with conventional heating. Microwave irradiation of the THF reaction mixture normally generated pressures of 8−10 bar at 160 °C (12−15 bar at 180 °C), and because of the unavailability of a high-pressure equipment using conventional heating, these high-pressure experiments were conducted with microwave synthesizers, which provided the required safe environment.

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