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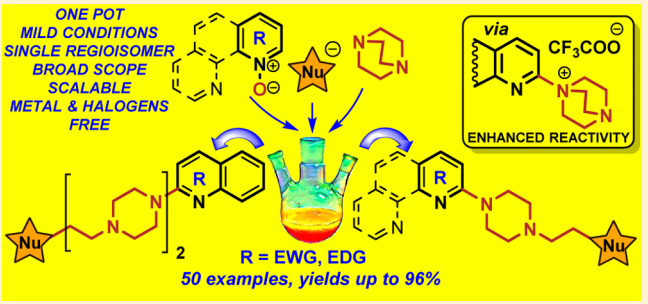
Quaternary *N*-(2-Pyridyl)-DABCO Salts: One-Pot in Situ Formation from Pyridine-*N*-oxides and Reactions with Nucleophiles: A Mild and Selective Route to Substituted *N*-(2-Pyridyl)-*N*′-ethylpiperazines

Dmitry I. Bugaenko, Marina A. Yurovskaya, and Alexander V. Karchava*

Department of Chemistry, Moscow State University, Moscow 119992, Russia

Supporting Information

ABSTRACT: The *N*-(2-pyridyl)-*N*′-ethylpiperazines are important structural motifs in several medicinally relevant compounds. Known synthetic methods toward these structures are multistep and generally based on the S_NAr-chemistry; their applicability is significantly limited to substrates containing electron-withdrawing groups. Here, we describe a new methodology for a rapid and modular access to this privileged scaffold. Importantly, the developed protocol proved to be very general and efficient for the substrates containing substituents of different electronic nature. An operationally simple, metal-free, one-pot synthetic procedure involves the initial reaction of activated heterocyclic *N*-oxides with DABCO, followed by in situ treatment of the resultant quaternary *N*-(2-pyridyl)-DABCO salts with nucleophiles, resulting in ring-opening. The method features mild reaction conditions, high positional selectivity, and excellent functional-group tolerance. The utility of our approach is demonstrated by the late-stage site-selective functionalizations of complex molecules; a rapid modular assembly of MC2050, a potent PARP-1 inhibitor; and gram-scale preparations.



INTRODUCTION

Pyridines and piperazines are among the most frequently utilized nitrogen heterocycles in FDA approved drugs.[1,2] Also, substituted pyridines[3] and piperazines[4−6] have found widespread application as experimental drugs, agrochemicals, ligands, and functional materials. Because of their important role in many fields, methods to access diversely functionalized derivatives of these privileged heterocycles have been highly sought after.[7]

The *N*-heteroaryl-*N*′-ethylpiperazine motif is an essential structural component of several marketed drugs and drug candidates. Among them are Spycel[8] and Geodon,[4] the approved drugs for treatments of cancer and schizophrenia, respectively. Particularly, the *N*-(2-pyridyl)-*N*′-ethylpiperazine fragment can be found in potent PARP-1,[9,10] SMO,[11] and PI3K[12] inhibitors, and a promising experimental drug for the treatment of neurodegenerative disorders (Figure 1).[13] Traditional synthetic strategies toward these compounds rely upon a nucleophilic substitution in electron-deficient heterocyclic halides with the appropriate piperazine precursors. However, the scope of this approach is often dramatically restricted due to costly substituted heteroaryl halides and the lack of *N*-monosubstituted piperazines; both compounds are usually accessed via multistep sequences. Another approach to this type of compounds is based on transition-metal-catalyzed C−N-bond forming reactions and uses the same not readily available starting materials and additionally requires expensive and toxic catalysts and supporting ligands.[6,14,15]

Alternatively, reactions between 2-halopyridines or derivatives thereof and 1,4-diazabicyclo[2.2.2]octane (DABCO) could generate the quaternary ammonium salts **A** (Y = Hal) (Scheme 1), which would react with nucleophiles affording *N*-(2-pyridyl)-*N*′-ethylpiperazines via a ring-opening reaction. From this perspective, the ammonium salts **A** could be extremely valuable intermediates to furnish medicinally relevant heterocyclic scaffolds in a modular and step-economical manner. However, due to the harsh reaction conditions required, salt **A** has never been prepared using the S_NAr-based approach, but instead piperazines **B** and **C** comprising substituted *N*-ethylpiperazinyl moiety have been reported to be isolated, which presumably originated from ring-opening of the initially formed salts **A** (Y = Cl, Scheme 1).[16−20] Although the use of *N*-(2-chloroethyl)piperazines **C** as substrates in reaction with nucleophiles has been revealed, nevertheless, the protocol demands high reaction temperatures (>160 °C) for their generation and the further elaboration, resulting in the restricted functional group compatibility.[17,20] Finally, this method is only applicable to pyridines bearing electron-withdrawing groups such as NO_2, CF_3, CN, and CO_2R; no reaction products were detected with 2-chloropyridine and 2-chloro-4-picoline as the starting materials.[20] Thus, incorporation of pyridines without electron-withdrawing groups remains challenging. To address this limitation, obviously, the

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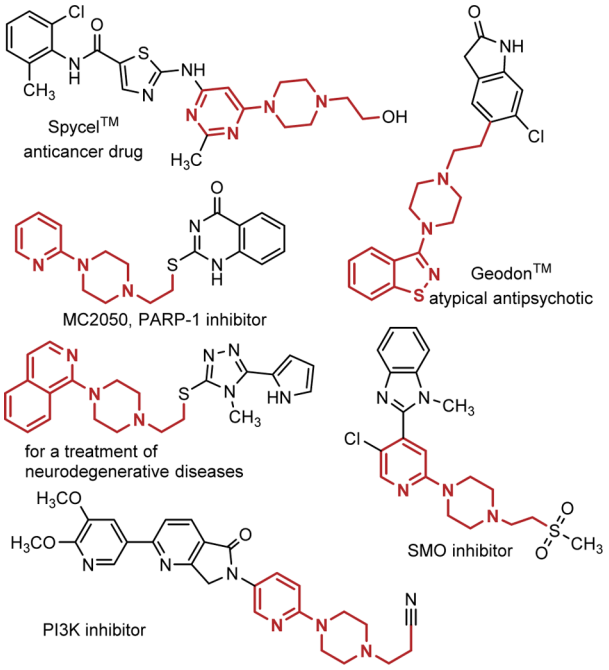
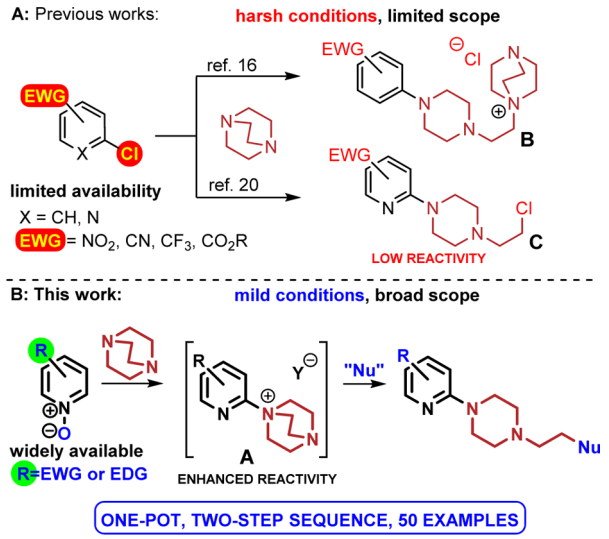


Figure 1. Representative examples of marketed drugs and drug candidates containing *N*-heteroaryl-*N*′-ethylpiperazine core.

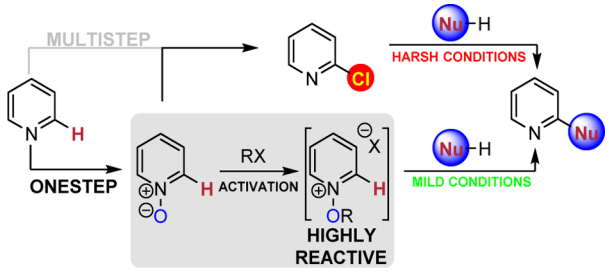
Scheme 1. Strategy for *N*-(Hetero)aryl-*N*-ethylpiperazine Synthesis Using DABCO



other type of reaction should be used to produce the quaternary salts **A**.

Pyridine-*N*-oxides preactivated with acylating agents are ideal substrates in the reactions with a broad range of nucleophiles offering a valuable synthetic alternative to the nucleophilic substitution in 2-halopyridines and transition-metal-catalyzed reactions.[21−23] Nucleophilic displacement in 2-halopyridines is the strongly substrate-dependent reaction and typically requires harsh conditions,[24] resulting in limited substrate scope and low functional group tolerance. To the contrary, addition of a nucleophile to an activated pyridine-*N*-oxide (generally prepared in situ) and the subsequent deoxygenative aromatization usually proceed efficiently under mild conditions, which improves functional group tolerance and overall applicability of the process. Furthermore, halo-pyridines are not easily accessible in a regioselective mode and are normally prepared from the corresponding *N*-oxides, which in turn can be easily obtained in high yields via simple oxidation of commercially available pyridines (Scheme 2).[24]

Scheme 2. S_NAr- and *N*-Oxide-Based Approaches to 2-Substituted Pyridines



Although known for almost one-half of a century,[23] the *N*-oxide-based strategy for the synthesis of substituted pyridines has received significant attention in recent years. Many reliable synthetic protocols for the preparation of substituted pyridines and fused pyridines from the *N*-oxide precursors have been developed. Various nucleophiles including halogenide-,[25−28] azide-ions,[29] amines,[30−33] *NH*-heterocycles,[34,35] alcohols[36] and phenols,[35] thiols and thiophenols,[35] as well as carbon nucleophiles (enamines,[37] silyl ketene acetals,[38] and azalactones[39]) were successfully employed under mild and metal-free reaction conditions with a significantly larger scope of substrates in contrast to the conventional S_NAr-based approach. An intramolecular version of this process was used for the preparation of fused heterocycles via C−N[40] and C−O[41,42] bond formations. Despite the obvious advantages of this useful strategy, issues of low α/α' and α/γ selectivity as well as lack of generality often arise.[25,27] In fact, some methods for the preparation of fused pyridines (quinolines, isoquinolines, etc.) are not suitable to pyridines.[25,26] Therefore, new and broad applicable methods for regioselective conversion of readily available pyridine-*N*-oxides into substituted pyridines with wide functional group tolerance are of high interest. If developed effectively, these methods provide streamlined access to valuable scaffolds for pharmaceutical and agrochemical applications.

RESULTS AND DISCUSSION

Herein, we present the first synthetic access to *N*-(2-pyridyl)-*N*′-ethylpiperazines applicable to substrates bearing both electron-donating and electron-accepting groups in the heterocyclic moieties. Our strategy is based on a two-step sequence comprising the generation of *N*-(2-pyridyl)-DABCO salts **A** (Y = $CF_3CO_2^-$, Scheme 1) from pyridine-*N*-oxides and DABCO, followed by nucleophilic ring-opening accomplished in one pot (Scheme 1B). On the basis of the literature, two mechanistically distinct plausible pathways for the formation of the quaternary salt **A** can be proposed (Scheme 3). In both cases, initial activation of the *N*-oxide by trifluoroacetic anhydride leads to enhancing both electrophilicity and *CH*-acidity of the C-2 position. An attack of nucleophilic DABCO and the subsequent deprotonation/aromatization then provide the C-2 substituted product **A**, similar to the Reissert−Henze reaction[43] (pathway a).[25] Alternatively, the activated *N*-oxide can be deprotonated by DABCO to generate a highly active electrophilic species such as a carbene,[44,45] which in turns

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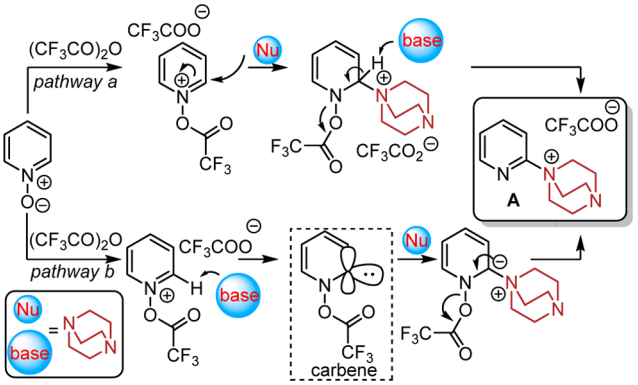
Scheme 3. Plausible Pathways for the Formation of the Quaternary Salt A



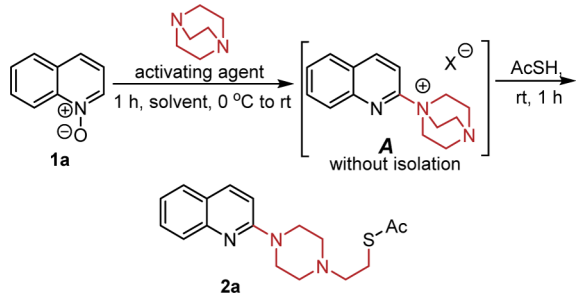
attacks a lone pair of DABCO. The subsequent aromatization in this case also provides the salt **A** (pathway b, Scheme 3).[28]

The key features of our approach include (1) the mild reaction conditions preventing the further transformation of salts **A** into compounds **B** and **C** (in contrast to the S_NAr-based approach, see Scheme 1A), and (2) the enhanced reactivity of salts **A** toward nucleophiles. Although there have been few reports on the preparation of 2-pyridyltrialkylammonium salts from pyridine-*N*-oxides and tertiary amines, their synthetic application was examined only in aromatic nucleophilic displacement of the trialkylammonium groups.[31,46] However, no studies have been reported on nucleophilic ring-openings of quaternary *N*-aryl-DABCO salts, and, in particular, on using the salts **A** for a broad scope synthesis of substituted *N*-(2-pyridyl)-*N*′-ethylpiperazines.

To optimize the reaction conditions, quinoline *N*-oxide (**1a**) and thioacetic acid (AcSH) were selected as a model substrate and a nucleophile, respectively. The reaction was designed as one-pot, two-step transformations toward substituted piperazines **2** including an intermediate formation of the quaternary ammonium salt **A** (Table 1). Initially, a mixture of the *N*-oxide **1a** and DABCO was treated with an activating agent to give the salt **A**, which was afterward quenched with AcSH.

Testing of different reaction parameters revealed that the highest yield of the desired piperazine **2a** was obtained when the reaction was performed in MeCN with 7 equiv of DABCO and trifluoroacetic anhydride (TFAA, 2.5 equiv) as the activating agent. Unacceptably low yields were observed with other typically used activating agents (Table 1, entries 1−6). Notably, the formation of the quaternary salt **A** ($X = CF_3CO_2^-$) was not highly solvent dependent: the starting material **1a** was completely consumed (TLC) within 1 h at the ambient temperature in all tested solvents. Although MeCN and DMF were preferred solvents providing near quantitative yields and high purity (GC−MS) of the piperazine **2a** even without a column chromatography, comparable yields were obtained in benzene and THF, while the yield was moderate in CH_2Cl_2 (entries 1, 7−10). Control experiments showed that using less than 7 equiv of DABCO as well as less than 2 equiv of TFAA resulted in decreasing yield (entries 1, 11−16). It should be mentioned that DABCO plays a dual role, acting as the nucleophile for the first step as well as a base for both the first and the second steps. Remarkably, under the mild reaction conditions employed, no bis-piperazine side product (similar to the salt **B**, Scheme 1A), arising from a nucleophilic attack of excess DABCO on the initially formed salt **A** was detected even

Table 1. Optimization of the Reaction Conditions[a]



entry	DABCO, equiv	activating agent, equiv	AcSH, equiv	solvent	yield, %[b]
		Activating Agent			
1	7	TFAA 2.5	4	MeCN	98
2	7	Ac_2O 2.5	4	MeCN	0
3	7	Ts_2O 2.5	4	MeCN	38
4	7	ClOCCOCl 2.5	4	MeCN	26
5	7	MeOCOCl 2.5	4	MeCN	0
6	7	TMSCl 2.5	4	MeCN	0
		Solvent			
7	7	TFAA 2.5	4	CH_2Cl_2	48
8	7	TFAA 2.5	4	THF	86
9	7	TFAA 2.5	4	DMF	99 (96)
10	7	TFAA 2.5	4	PhH	88
		Ratio of DABCO, TFAA, AcSH			
11	4.5	TFAA 1.5	2	MeCN	57
12	6	TFAA 2.5	3	MeCN	79
13	7	TFAA 2.5	3	MeCN	91
14	3	TFAA 2.5	3	MeCN	38[c]
15	6	TFAA 2.5	4	MeCN	81
16	7	TFAA 2.0	4	MeCN	94
17	12	TFAA 2.5	4	MeCN	98
		Time of the Reaction after Addition of AcSH			
18[d]	7	TFAA 2.5	4	MeCN	48
19[e]	7	TFAA 2.5	4	MeCN	71
20[f]	7	TFAA 2.5	4	MeCN	98 (96)

[a]Reactions were performed on 1 mmol (1 equiv) of quinoline *N*-oxide (**1a**) in 20 mL of solvent [0.05 M]. [b]Yields were determined with ^1H NMR using 3,6-dibromo-*p*-xylene as an internal standard. Yields in parentheses are isolated yields. [c]*N*,*N*-Diisopropylethylamine (4 equiv) was added. [d]Time of the reaction after addition AcSH was 15 min. [e]30 min. [f]60 min. DABCO = 1,4-diazabicyclo[2.2.2]octane, TFAA = trifluoroacetic anhydride.

with 12 equiv of DABCO (entry 17). In a separate set of experiments (entries 18−20), the optimal reaction time for the second step was determined. By monitoring reaction progress with ^1H NMR spectroscopy, we observed complete product formation within 1 h at room temperature. Finally, the reaction demonstrated an exceptional regioselectivity: only the 2-substituted quinoline **2a** (confirmed by 2D NMR experiments: NOESY and HMBC)[47] was obtained, and the corresponding 4-isomer was not detected.

Having established the optimal reaction conditions (Table 1, entries 1 and 9), we next studied the scope of *N*-oxides (Table 2). The method showed excellent generality for pyridine- and quinoline-*N*-oxides bearing electronically diverse substituents. Utilizing *N*-oxides of unsubstituted pyridine (**2b**), alkylpyridines (**2c** and **2e**), (hetero)arylpyridines (**2d**, **2f**, and **2l**), and aminopyridines (**2g** and **2k**) as substrates, the corresponding products were obtained in good to high yields as single

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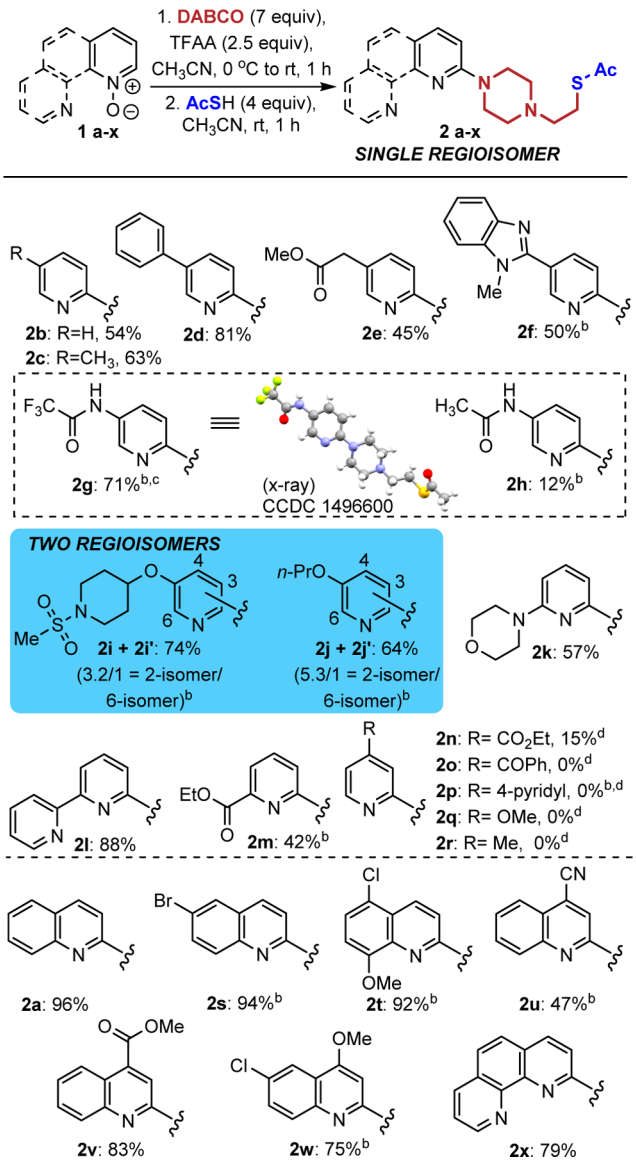
Table 2. Scope of Heterocyclic *N*-Oxides[a]



[a]Reactions were performed on 1 mmol (1 equiv) of *N*-oxide **1** in CH_3CN [0.05 M]. Yields are isolated yields. [b]DMF was used instead of MeCN. [c]Isolated from the reaction of **1h** as a result of transamidation. [d]See text.

regioisomers. Importantly, this method provides access to *N*-(2-pyridyl)-*N*′-ethylpiperazines, which are inaccessible through current methods based on the S_NAr chemistry.[20] Apart from two cases, installation of the piperazine moiety in 3-substituted pyridine-*N*-oxides occurred at the 6-position with the complete positional selectivity. Pyridine-*N*-oxides with alkoxy substituents at the 3-position **1i** and **1j** were exceptional substrates, leading under the standard reaction conditions to mixtures of the amination products at the 6- and 2-positions (**2i** + **2i**′ and **2j** + **2j**′). For both substrates, the sterically less hindered 6-regioisomers (**2i** and **2j**) were the major products, as confirmed by 2D NMR experiments (ROESY and HMBC).[47] Although the preferential attack of sterically demanding DABCO on the sterically less hindered 6-position is not surprising, the 2/6-selectivity observed for 3-alkoxysubstituted *N*-oxides **1i** and **1j** was unexpected and allowed us to assume that the steric hindrance is not the only factor governing selectivity; stereoelectronic interactions probably also contribute to the reaction outcome. Conversions of 4-substituted pyridine-*N*-oxides were less successful. Ethyl isonicotinate *N*-oxide (**1n**) and 4-bezoylpyridine *N*-oxide (**1o**) were unproductive under the standard conditions; only starting materials were fully recovered in both cases. When alternative reaction conditions (90 °C, 24 h) were applied in the first step, the targeted product **2n** was formed in a low yield (15%), with 67% of the starting *N*-oxide **1n** being recovered. Nevertheless, the *N*-oxide **1o** did not undergo the process even under these forcing reaction conditions. *N*-Oxides of 4-picoline (**1r**) and 4,4′-bipyridine (**1p**) gave only products of the des-oxygenation (in 38% and 94% yields, respectively), whereas neither the targeted piperazine **2q** nor the starting material were isolated when the reaction was performed with 4-metoxypyridine *N*-oxide (**1q**). Diversely substituted quinoline-*N*-oxides reacted smoothly, affording the expected products **2s**−**2x** as single C-2 isomers and in high yields. Notably, the bicyclic substrates **1v** and **1w** turned into the corresponding piperidines **2v** and **2w** in high yields unlike their monocyclic counterparts **1n** and **1q**. This difference presumably reflects the known increased reactivity of fused pyridine-*N*-oxides in reactions of this type, which we have mentioned previously.[21c,25,26] In general, many nucleophile-sensitive and synthetically valuable functional groups including halide, ether, ester, amide, and nitrile were perfectly tolerated under the used reaction conditions.

Next, other types of sulfur nucleophiles that can be applied for the ring-opening step were examined. Thiophenols, including *N*-unprotected 2-aminothiophenol, heterocyclic thiols, and benzylthiol, were found to be suitable partners delivering the corresponding piperazines in good to high yields under mild reaction conditions (Table 3). *SH*-Heterocycles, which were investigated as nucleophiles, are common in drug-like molecules.[48,49] Sodium benzenesulfinate gave the sulfone **3s** only in a modest yield. Quite surprisingly, the expected piperazine was not obtained when sodium thiocyanate was used as the nucleophile; salt **4a** was instead isolated in a very high yield. The structure of **4a** was unambiguously confirmed by X-ray diffraction analysis (Table 3). Salt **4a** obviously originated from a nucleophilic attack of excess DABCO onto the initially formed quaternary salt **A** (Table 1). In this case, thiocyanate-ion proved to be a weaker nucleophile as compared to DABCO.

On the basis of the above observation, we decided to explore the utility of our starting materials for the preparation of heterocyclic compounds comprising bis(ethylpiperazine) motif, which can be found in biologically active compounds[50,51] (Table 4). We hypothesized that suitable reaction conditions in the first step of the process would lead to the formation of ammonium salts **B** that would be reactive to the further ring opening. Increasing the reaction time and temperature (8 h, 90 °C) in the first and second steps under otherwise identical reaction conditions (compare to Table 1, entry 1) led to the formation of bis-piperazine **5a** in 83% yield. Other sulfur nucleophiles as well as sodium azide similarly underwent this process; bis-piperazines **5b**−**5d** were afforded in good to high yields (61−79%) through a one-pot procedure. It is worth mentioning that the preparation of compounds **5**, employing the synthetic methods reported to date, would require multistep sequences including protection/deprotection operations.[50,51]

Having explored the scope of sulfur nucleophiles in the ring-opening reactions of the quaternary *N*-(2-pyridyl)DABCO

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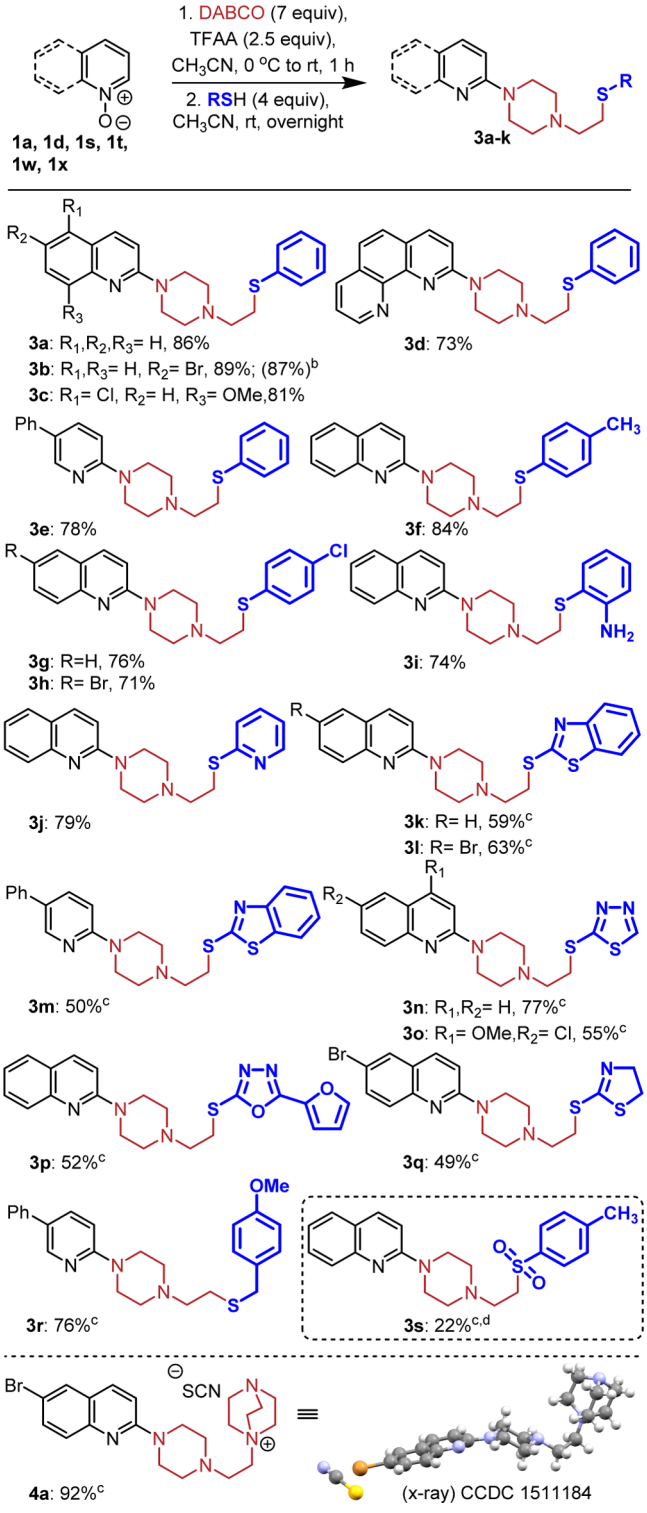
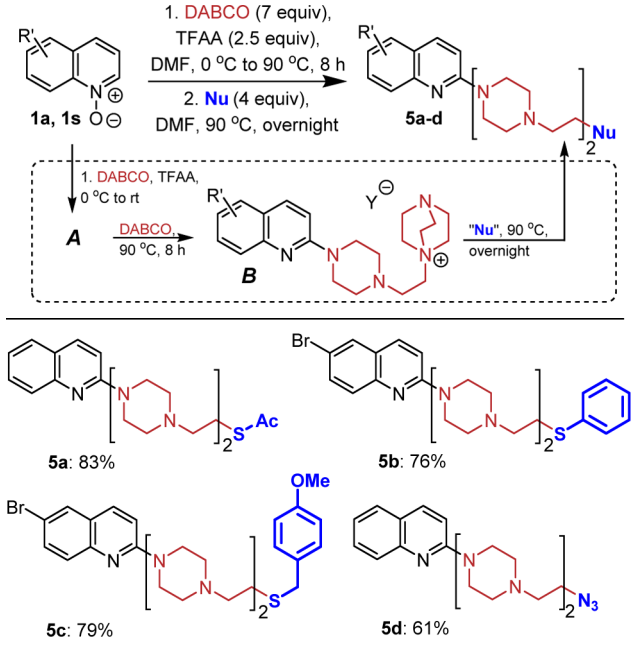
Table 3. Scope of Sulfur Nucleophiles[a]



[a]Reactions were performed on 1 mmol (1 equiv) of *N*-oxide **1** in CH_3CN [0.05 M]. Yields are isolated yields. [b]12 equiv of DABCO was used. [c]DMF was used. [d]Sodium *p*-toluenesulfinate was employed, 90 °C in the second step.

Table 4. Synthesis of Bis-piperazines[a]



[a]Reactions were performed on 1 mmol (1 equiv) of *N*-oxide **1** in DMF [0.05 M]. Yields are isolated yields.

salts, we turned our attention to other types of nucleophiles (Table 5). Although slightly higher temperature and prolonged reaction time were required, the quaternary salt **A** demonstrated a high level of reactivity toward nitrogen, carbon, and oxygen nucleophiles. We found that potassium phthalimide, methylhydrazine, morpholine, and sodium cyanide take part in the ring-opening process smoothly to afford the expected piperazine compounds **6a**−**6d** chemo- and regioselectively in good yields (54−84%). Sodium azide gave under the same reaction condition an inseparable mixture of piperazine **6e** and tetrazolo[1,5*a*]quinoline (**7e**) in a 1:1 ratio. Furthermore, the reaction of sodium 4-fluorophenolate failed to produce the expected piperazine **6f** and resulted in the formation of 2-phenoxyquinoline **7f** exclusively. Apparently, the observed reaction outcome can be explaining and predicted considering hard−soft properties[52] of the used nucleophiles. For the relatively soft nucleophiles, such as thiols, amines, and cyanide-ion, the preference to form piperazines as a result of the nucleophilic attack on the quaternized DABCO moiety is considerably greater. In contrast, the harder nucleophiles, such as phenolate, tend to react at the C-2 position of quinoline bringing about a nucleophilic displacement of DABCO as a leaving group. The earlier report on the synthesis of 2-fluoropyridines via nucleophilic substitution in 2-pyridyltrialkylammonium salts with "hard" fluorine anion complements our observations.[31]

With the developed protocol, we next demonstrated its synthetic utilities. First, we applied our method for the late-stage functionalization[53] of Quinoxyfen, an active ingredient of many fungicides (Scheme 4A).[54] Quinoxyfen was oxidized, and the corresponding *N*-oxide **1y**[55] was successfully subjected to our standard reaction conditions (Table 1, entry 1) to afford the piperazine **8** in 68% yield (56% yield over two steps starting from Quinoxyfen). Furthermore, our standard reaction conditions were employed for modification of the bis-*N*-oxide **1z** containing two alkylated pyridine moieties. Interestingly, the isomerically substituted pyridine rings reacted in different ways: while the 3-alkylpyridine part reacted in the typical manner, producing a substituted piperazine, the 2-alkypyridine fragment underwent the Boekelheide reaction,[56] to provide after hydrolysis introduction of the hydroxyl group (Scheme 4B).

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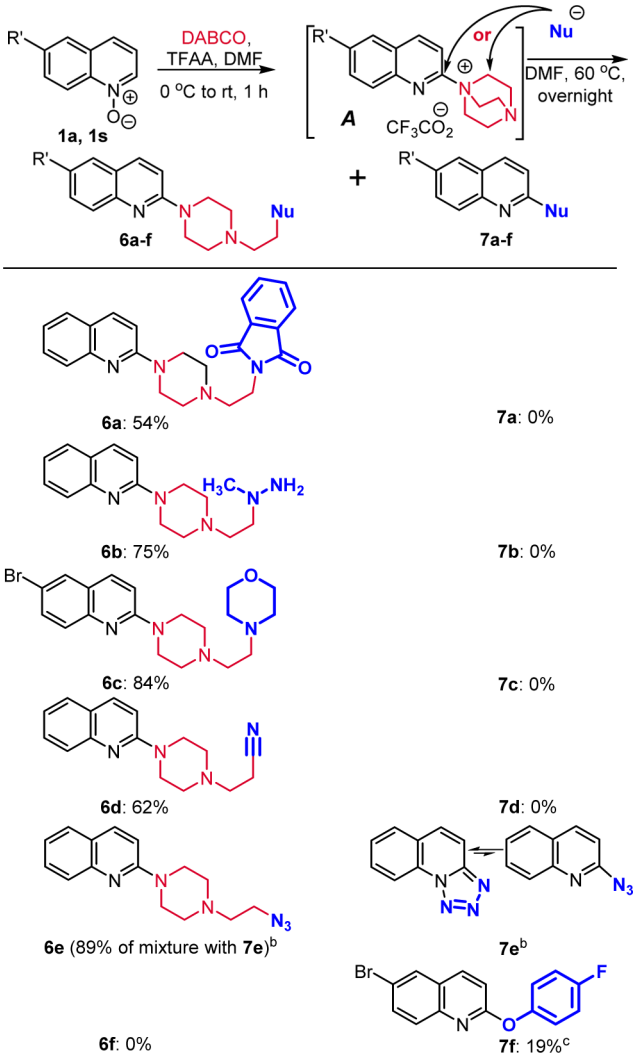
Table 5. Scope of Other Nucleophiles[a]

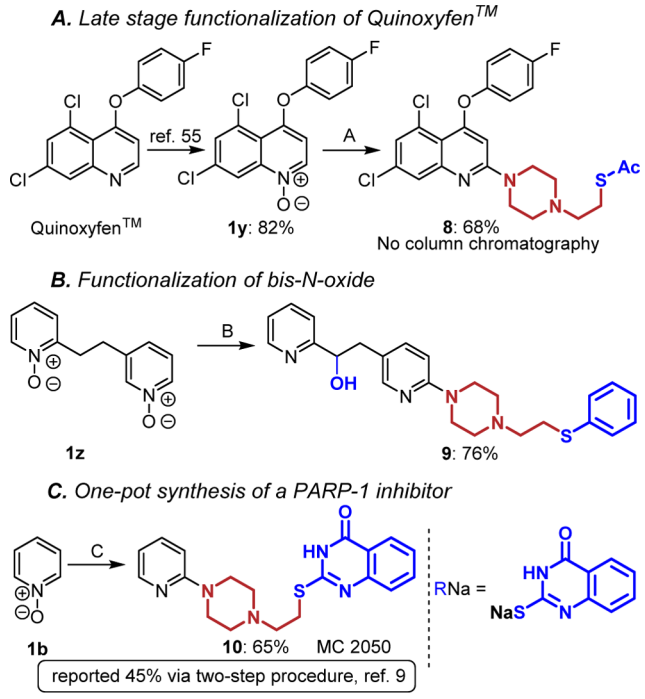


[a]Reactions were performed on 1 mmol (1 equiv) of *N*-oxide **1** in DMF [0.05 M]: (1) DABCO (7 equiv), TFAA (2.5 equiv); (2) nucleophile (4 equiv). Yields are isolated yields. [b]Obtained as a mixture (1:1), 89% total yield. [c]Not optimized.

Overall, utilizing a simple, one-pot procedure, the complex heterocyclic compound **9** was obtained in excellent yield (76%) and complete regioselectivity. This transformation is particularly appealing due to the selectivity and the rapid installation of molecular complexity, gained through the one-pot procedure. Finally, we focused on the streamlined one-pot synthesis of MC2050 (**10**), a potent PARP-1 inhibitor, from readily available pyridine *N*-oxide (**1b**) and 2-mercapto-4(3*H*)-quinazolinone. Our innovative approach provided the targeted agent **10** in 65% yield (Scheme 4C). Previously reported preparation of this compound includes a two-step sequence, affording MC2050 (**10**) in 45% overall yield.[9]

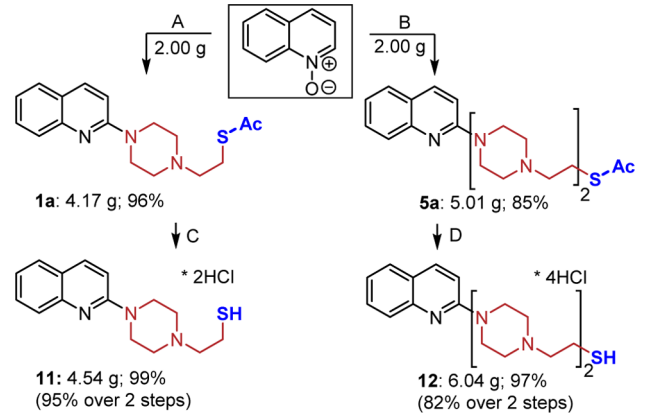
To highlight the practicality and robustness of the presented method, synthetically useful thiols **11** and **12** were prepared in gram-scale, employing quinoline *N*-oxide and DABCO as the common starting materials and slightly different reaction conditions. Thiols **11** and **12** were obtained in high overall yields (95% and 82%, respectively) and purity without chromatography purification (Scheme 5).

Scheme 4. Synthetic Application[a]



[a]Yields are isolated. Reaction conditions: (A) (1) *N*-oxide (**1y**, 1 mmol, 1 equiv), DABCO (7 equiv), TFAA (2.5 equiv), CH_3CN [0.05 M], 0 °C to rt, 1 h; (2) AcSH (4 equiv), rt, 1 h; (B) (1) *N*-oxide (**1z**, 1 mmol, 1 equiv), DABCO (10 equiv), TFAA (5 equiv), CH_3CN [0.05 M], 0 °C to rt, 10 h; (2) PhSH (6 equiv), rt, 10 h; (3) 2 M Na_2CO_3, rt, 3 h; (C) (1) *N*-oxide (**1b**, 1 mmol, 1 equiv), DABCO (7 equiv), TFAA (2.5 equiv), DMF [0.05 M], 0 °C to rt, 1 h; (2) K_2CO_3 (5 equiv), rt, 0.5 h; (3) RNa (4 equiv), rt, overnight.

Scheme 5. Scale-up Preparations[a]



[a]Yields are isolated yields. Conditions: (A) see Table 2; (B) see Table 4; (C) AcCl (6 equiv), MeOH [0.21 M], rt, 24 h; (D) AcCl (8 equiv), MeOH [0.21 M], rt, 24 h.

CONCLUSION

This work represents the first systematic investigation on the generation of quaternary *N*-(2-pyridyl)DABCO salts from substituted pyridine-*N*-oxides and their previously unexplored reactivity with nucleophiles. Reaction of activated *N*-oxides with DABCO proceeds rapidly and in a regioselective manner under mild conditions. In situ generated salts react with sulfur, nitrogen, and carbon nucleophiles via a ring-opening pathway,

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providing concise access to substituted *N*-ethylpiperazines in good to high yields, including compounds inaccessible by other methods. Overall, the one-pot, two-step process is applicable to a wide variety of structurally and electronically diverse substrates and nucleophiles and tolerant to many different functionalities. The high synthetic potential of the method was proved by the synthesis of biologically relevant compounds, including MC2050, a potent PARP-1 inhibitor, the late-stage functionalization of Quinoxyfen, as well as gram-scale preparations. Interestingly, unlike the above-mentioned nucleophiles, phenolate-ion reacts yielding a product of the nucleophilic displacement of the DABCO-moiety rather than the ring opening.

EXPERIMENTAL SECTION

General Information. All commercially available chemicals and solvents of high purity were used without purification unless otherwise stated. Thioacetic acid was distillated prior to use. DABCO was used from a freshly opened bottle. Column chromatography was performed in flash conditions using silica gel (0.040−0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on silica gel 60 F254 plates that were visualized by exposure to UV light. ^{1}H and ^{13}C NMR were recorded at 400 or 600 MHz and 75, 100, or 150 MHz, respectively, for solutions in $CDCl_3$, DMSO-d_6, or D_2O. Chemical shifts are quoted in δ (ppm), and J values are reported in Hz. Chemical shifts are referenced relative to residual proton signals of the deuterated solvents. Mass-spectra were recorded by EI mode with 70 eV. High-resolution mass spectra (HRMS) were measured using electrospray ionization (ESI) on an Orbitrap spectrometer. FT-IR spectra were measured in KBr or as neat compounds. Only characteristically absorption bands were described, which are given in wave numbers (cm^{-1}). Melting points were determined in open capillaries and are uncorrected. Reactions to produce product of types **2**−**11** were run under an argon atmosphere. Yields refer to chromatographically and spectroscopically pure compounds.

Methylpyridin-3-ylacetate. This was prepared following the literature procedure.[57] Characterization data obtained matched those previously reported in the literature.[57] ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.3, 150.5, 148.7, 136.9, 129.8, 123.5, 52.4, 38.4.

1-Methyl-2-pyridin-3-yl-1*H*-benzimidazole. To a stirred solution of 2-pyridin-3-yl-1*H*-benzimidazole[58] (3.90 g, 20 mmol, 1 equiv) in DMF (30 mL, 0.67 M) was added sodium hydride (60 w/w dispersion in mineral oil, 960 mg, 24 mmol, 1.2 equiv) portionwise over 30 min at 0 °C. After the mixture was stirred for 1 h at rt, dimethyl sulfate (2.77 g, 2.1 mL, 22 mmol, 1.1 equiv) was added dropwise over 30 min. The reaction mixture was stirred for 1 h, and the solvent was removed under reduced pressure. The residue was dissolved in 60 mL of CH_2Cl_2 and washed with 2 M aq NaOH (2 × 40 mL) and then with H_2O (6 × 40 mL). The organic layers were dried with Na_2SO_4, and the solvent was removed under reduced pressure to give the desired product as a tan solid, yield 3.90 g (93%); mp: 140−143 °C. Characterization data obtained matched those previously reported in the literature.[59]

5-Chloro-8-methoxyquinoline. This was prepared from 5-chloro-8-hydroxyquinoline (3.59 g, 20 mmol) using the procedure described for 1-methyl-2-pyridin-3-yl-1*H*-benzimidazole. Yellow solid; yield 3.77 g (97%); mp: 60−63 °C. Characterization data obtained matched those previously reported in the literature.[60]

3-Phenylpyridine 1-Oxide (1d),[61] 4-(1-Oxidopyridin-2-yl)-morpholine (1k),[62] 2-Pyridin-2-ylpyridine 1-Oxide (1l),[63] Ethyl-pyridine-2-carboxylate 1-Oxide (1m),[64] Ethyl Isonicotinate 1-Oxide (1n),[64] (1-Oxidopyridin-4-yl) (Phenyl)methanone (1o),[65] 4-Methoxypyridine 1-Oxide (1q),[66] 6-Bromoquinoline 1-Oxide (1s),[55] 5-Chloro-8-methoxyquinoline 1-Oxide (1t),[60] Methyl Quinoline-4-carboxylate 1-Oxide (1v),[67] 1,10-Phenanthroline 1-Oxide (1x),[68] and 5,7-Dichloro-4-(4-fluorophenoxy)quinoline 1-Oxide (1y).[55] These were prepared using reported procedures. Characterization data obtained for these compounds matched those previously reported in the literature.

General Procedure for the Synthesis of Heterocyclic N-Oxides (General Procedure A). To a cooled to 0 °C and stirred solution of a heterocyclic compound (15 mmol, 1 equiv) in CH_2Cl_2 (40 mL, 0.375 M) was slowly added *m*-CPBA (75%, 4.14 g, 18 mmol, 1.2 equiv), and stirring was continued for 24 h at rt. Saturated aqueous solution of K_2CO_3 was slowly added, the resulting mixture was stirred for 30 min, then the layers were separated, and the water layer was extracted well with $CHCl_3$ (5 × 30 mL). The combined organic layers were dried with Na_2SO_4, and the solvent was removed under reduced pressure to give the desired product in a high purity. The products were used in the next step without additional purification.

Do not remove the solvent immediately after the end of the reaction under reduced pressure, as it is very dangerous!

*Methyl (1-Oxidopyridin-3-yl)acetate (**1e**).* Yield 2.23 g (89%); amorphous; light yellow. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (s, 1H), 8.10−8.12 (m, 1H), 7.18−7.24 (m, 2H), 3.70 (s, 3H), 3.57 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.5, 139.2, 137.3, 133.0, 127.3, 125.3, 51.9, 37.0. MS, *m*/*z* (I, %): 167 (100, M^+), 151 (63), 92 (96). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{10}NO_3$, 168.0655; found, 168.0657.

*1-Methyl-2-(1-oxidopyridin-3-yl)-1H-benzimidazole (**1f**).* Yield 3.44 g (76%); amorphous; light yellow. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.63 (s, 1H), 8.33 (d, J = 6.6 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.35−7.48 (m, 4H), 3.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 142.5, 139.5, 139.0, 136.5, 129.9, 126.3, 126.0, 123.9, 123.0, 120.1, 109.9, 31.7. MS, *m*/*z* (I, %): 225 (M^+, 83), 209 (53), 208 (100), 156 (63). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{12}N_3O$, 226.0975; found, 226.0979.

*N-(1-Oxidopyridin-3-yl)acetamide (**1h**).* Yield 2.98 g (98%); white solid; mp: 208−211 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (br, 1H), 8.63 (s, 1H), 7.74 (d, J = 6.4 Hz, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.00−7.04 (m 1H), 1.97 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 169.1, 138.3, 133.4, 129.8, 126.1, 115.6, 23.8. MS, *m*/*z* (I, %): 152 (M^+, 100), 110 (54), 94 (32), 93 (44). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_7H_9N_2O_2$, 153.0659; found, 153.0657.

*3-{[1-(Methylsulfonyl)piperidin-4-yl]oxy}pyridine 1-Oxide (**1i**).* Yield 5.16 g (95%); white solid; mp: 118−121 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.95 (d, J = 6.1 Hz, 1H), 7.18−7.23 (m, 1H), 6.95 (d, J = 8.4 Hz, 1H), 4.47−4.53 (m, 1H), 3.22−3.33 (m, 4H), 2.76 (s, 3H), 1.83−2.05 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.5, 132.5, 129.0, 125.9, 116.6, 72.3, 42.1, 34.8, 29.5. MS, *m*/*z* (I, %): 272 (M^+, 33), 162 (100), 112 (27), 84 (44), 55 (33). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{11}H_{17}N_2O_4S$, 273.0904; found, 273.0907.

*3-Propoxypyridine 1-Oxide (**1j**).* Yield 2.89 g (94%); yellow viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.96−7.98 (m, 1H), 7.17−7.21 (m, 1H), 6.93−6.95 (m, 1H), 3.92−3.96 (m, 2H), 1.77−1.86 (m, 2H), 1.01−1.04 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 131.1, 127.1, 125.1, 114.6, 69.8, 21.2, 9.30. MS, *m*/*z* (I, %): 153 (M^+, 81), 139 (47), 111 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_8H_{12}NO_2$, 154.0863; found, 154.0860.

*Quinoline-4-carbonitrile 1-Oxide (**1u**).* Yield 2.40 g (94%); yellow solid; mp: 183−185 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 8.4, 1H), 8.51 (d, J = 6.4, 1H), 8.22 (d, J = 8.4, 1H), 7.83−7.90 (m, 2H), 7.67 (d, J = 6.4 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 142.1, 135.1, 131.8, 131.1, 129.0, 126.3, 125.9, 120.2, 115.5, 106.3. MS, *m*/*z* (I, %): 170 (M^+, 100), 154 (22), 142 (26), 115 (70), 114 (25). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_7N_2O$, 171.0553; found, 171.0549.

*6-Chloro-4-methoxyquinoline 1-Oxide (**1w**).* Yield 3.06 g (97%); light-brown solid; mp: 209−212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 9.3 Hz, 1H), 8.46 (d, J = 6.4 Hz, 1H), 8.18 (d, J = 2.0, 1H), 7.72 (dd, J = 9.3, 2.0 Hz, 1H), 6.66 (d, J = 6.4 Hz, 1H), 4.06 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 139.0, 135.9, 133.9, 131.1, 122.9, 121.4, 121.3, 100.4, 56.1. MS, *m*/*z* (I, %): 211, 209 (M^+; 39, 100), 196, 194 (31, 96). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{10}H_9ClNO_2$, 212.0287 and 210.0316; found, 212.0287 and 210.0315.

*2-[2-(1-Oxidopyridin-3-yl)ethyl]pyridine 1-Oxide (**1z**).* This was prepared using 2.4 equiv of *m*-CPBA in 88% yield (2.85 g); off-white solid; mp: 184−187 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.27 (d, J =

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6.1 Hz, 1H), 8.03−8.09 (m, 2H), 7.09−7.19 (m, 5H), 3.18−3.21 (m, 2H), 3.06−3.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.6, 139.9, 139.6, 138.8, 137.0, 126.2, 126.1, 125.5, 125.4, 124.2, 31.8, 28.4. MS, *m*/*z* (I, %): 216 (M^+, 10), 199 (100), 181 (56). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{12}H_{13}N_2O_2$, 217.0972; found, 217.0970.

General Procedure for the Synthesis of Compounds ***2*** *(Table 2, General Procedure B).* To a solution of heterocyclic *N*-oxide **1a**−**y** (1 mmol, 1 equiv) in 20 mL (0.05 M) of CH_3CN (or DMF for *N*-oxides insoluble in CH_3CN: **1f**, **1h**, **1p**, **1s**, **1t**, **1u**, **1w**) was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 784 mg, 7 mmol, 7 equiv) in one portion. To the mixture cooled to 0 °C was added a solution of trifluoroacetic anhydride (525 mg, 350 μL, 2.5 mmol, 2.5 equiv) in CH_3CN (5 mL) dropwise. The resulted mixture was stirred for 1 h at rt. A solution of a thioacetic acid (304 mg, 4 mmol, 4 equiv) in CH_3CN (5 mL) was slowly added, and the resulting mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of CH_2Cl_2 and was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL), water layers were combined and extracted CH_2Cl_2 (4 × 20 mL), all organic layers were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel using gradient mixtures of EtOAc−*n*-hexane (1:4 to 1:0) or CH_2Cl_2−MeOH (20:1 to 2:1) as eluent.

S-[2-(4-Quinolin-2-ylpiperazin-1-yl)ethyl] Ethanethioate ***(2a)****.* Yield 0.303 g (96%); also was prepared following the general procedure using 2 g (13.8 mmol) of *N*-oxide **1a**; yield 4.17 g (96%); off-white solid; mp: 98−101 °C; R_f = 0.33 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.59 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.53 (t, *J* = 7.7, 1H), 7.22 (t, *J* = 7.5, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 3.75−3.79 (m, 4H), 3.06−3.10 (m, 2H), 2.60−2.66 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 157.3, 147.8, 137.6, 129.6, 127.3, 126.7, 123.2, 122.5, 109.6, 57.6, 52.9, 45.0, 30.7, 26.2. FT-IR (KBr): ν_{max} (cm^{-1}) 1691 (C═O). MS, *m*/*z* (I, %): 315 (M^+, 8), 240 (99), 171 (52), 157 (100), 128 (33). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{22}N_3OS^+$, 316.1478; found, 316.1480.

S-[2-(4-Pyridin-2-ylpiperazin-1-yl)ethyl] Ethanethioate ***(2b)****.* Yield 0.142 g (54%); amorphous; brown; R_f = 0.17 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, *J* = 6.0 Hz, 1H), 7.45−7.49 (m, 1H), 6.60−6.65 (m, 2H), 3.54−3.57 (m, 4H), 3.04−3.08 (m, 2H), 2.59−2.64 (m, 6H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 159.4, 147.9, 137.5, 113.4, 107.1, 57.5, 52.7, 45.1, 30.6, 26.3. FT-IR (thin film): ν_{max} (cm^{-1}) 1690 (C═O). MS, *m*/*z* (I, %): 265 (M^+, 6), 190 (100), 147 (36), 121 (56), 107 (78). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{13}H_{20}N_3OS^+$, 266.1322; found, 266.1332.

S-{2-[4-(5-Methylpyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate ***(2c)****.* Yield 0.175 g (63%); amorphous; brown; R_f = 0.19 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (s, 1H), 7.26 (d, *J* = 8.6 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 3.43−3.46 (m, 4H), 2.99−3.03 (m, 2H), 2.53−2.58 (m, 6H), 2.29 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 158.0, 147.6, 138.4, 122.3, 107.0, 57.5, 52.7, 45.6, 30.6, 26.3, 17.3. FT-IR (thin film): ν_{max} (cm^{-1}) 1690 (C═O). MS, *m*/*z* (I, %): 279 (M^+, 16), 204 (92), 190 (30), 135 (40), 121 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{14}H_{22}N_3OS^+$, 280.1478; found, 280.1483.

S-{2-[4-(5-Phenylpyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate ***(2d)****.* Yield 0.276 g (81%); beige solid; mp: 107−110 °C; R_f = 0.27 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.52−7.53 (m, 2H), 7.40−7.44 (m, 2H), 7.30−7.33 (m, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 3.62−3.70 (m, 4H), 3.09−3.11 (m, 2H), 2.64−2.72 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 158.6, 146.1, 138.3, 136.1, 128.9, 126.8, 126.3, 126.2, 106.8, 57.5, 52.6, 45.1, 30.6, 26.2. FT-IR (KBr): ν_{max} (cm^{-1}) 1686 (C═O). MS, *m*/*z* (I, %): 341 (M^+, 18), 266 (63), 197 (36), 183 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{24}N_3OS^+$, 342.1635; found, 342.1641.

Methyl (6-{4-[2-(Acetylthio)ethyl]piperazin-1-yl}pyridin-3-yl)-acetate ***(2e)****.* Yield 0.152 g (45%); brown solid; mp: 77−80 °C; R_f = 0.13 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, *J* = 2.3 Hz, 1H), 7.42 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.62 (d, *J* = 8.8 Hz, 1H), 3.67 (s, 3H), 3.52−3.57 (m, 4H), 3.48 (s, 2H), 3.04−3.08 (m, 2H), 2.59−2.64 (m, 6H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 172.1, 158.7, 148.2, 138.5, 118.8, 107.0, 57.6, 52.7, 52.1, 45.2, 37.5, 30.7, 26.3. FT-IR (KBr): ν_{max} (cm^{-1}) 1739 (C═O), 1680 (C═O). MS, *m*/*z* (I, %): 337 (M^+, 2), 193 (52), 179 (100), 162 (67). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_3S^+$, 338.1533; found, 338.1531.

S-(2-{4-[5-(1-Methyl-1H-benzimidazol-2-yl)pyridin-2-yl]piperazin-1-yl}ethyl) Ethanethioate ***(2f)****.* Yield 0.197 g (50%); light-brown solid; mp: 118−120 °C; R_f = 0.15 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.55 (d, *J* = 2.3 Hz, 1H), 7.99 (dd, *J* = 8.9, 2.3 Hz, 1H), 7.80−7.81 (m, 1H), 7.37−7.39 (m, 1H), 7.30−7.32 (m, 2H), 6.78 (d, *J* = 8.9 Hz, 1H), 3.89 (s, 3H), 3.72−3.75 (m, 4H), 3.10−3.12 (m, 2H), 2.66−2.70 (m, 6H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 159.1, 151.9, 148.3, 142.8, 138.5, 136.5, 122.5, 122.3, 119.2, 115.0, 109.5, 106.4, 57.4, 52.5, 44.7, 31.7, 30.6, 26.2. FT-IR (KBr): ν_{max} (cm^{-1}) 1689 (C═O). MS, *m*/*z* (I, %): 395 (M^+, 28), 320 (100), 237 (90). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{26}N_5OS^+$, 396.1853; found, 396.1840.

S-[2-(4-{5-[(2,2,2-Trifluoroacetyl)amino]pyridin-2-yl}piperazin-1-yl)ethyl] Ethanethioate ***(2g)****.* This wwas obtained from *N*-oxide **1h** together with **2h**. Yield 0.266 g (71%); light-brown solid; mp: 149−152 °C; R_f = 0.13 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.81−7.85 (m, 2H), 6.66 (d, *J* = 9.3, 1H), 3.56−3.66 (m, 4H), 3.08−3.12 (m, 2H), 2.66−2.74 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 156.5 (q, J_{CF} = 36.9 Hz), 155.2, 140.9, 131.4, 123.0, 115.9 (q, J_{CF} = 288.3 Hz), 106.8, 57.3, 52.4, 45.0, 30.5, 26.1. FT-IR (KBr): ν_{max} (cm^{-1}) 3295 (NH), 1713 (C═O), 1668 (C═O), 1141 (CF_3). MS, *m*/*z* (I, %): 376 (M^+, 6) 301 (100), 287 (50), 258 (46), 232 (96), 218 (80), 116 (55). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{20}F_3N_4O_2S^+$, 377.1254; found, 377.1242.

S-(2-{4-[5-(Acetylamino)pyridin-2-yl]piperazin-1-yl}ethyl) Ethanethioate ***(2h)****.* This was obtained from *N*-oxide **1h** together with **2g**. Yield 0.040 g (12%); light-brown solid; mp: 129−132 °C; R_f = 0.38 ($CHCl_3$/C_2H_5OH = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, *J* = 2.3, 1H), 7.83 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.18 (br, 1H), 6.63 (d, *J* = 9.2 Hz, 1H), 3.51−3.58 (m, 4H), 3.06−3.09 (m, 2H), 2.60−2.66 (m, 6H), 2.34 (s, 3H), 2.15 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 168.8, 157.0, 140.5, 131.7, 125.7, 107.2, 57.6, 52.7, 45.6, 30.7, 26.3, 24.2. FT-IR (KBr): ν_{max} (cm^{-1}): 3304 (NH), 1683 (C═O), 1655 (C═O). MS, *m*/*z* (I, %): 322 (M^+, 4), 247 (68), 207 (34), 178 (56), 164 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{23}N_4O_2S^+$, 323.1536; found, 323.1527.

S-{2-[4-(5-{[1-(Methylsulfonyl)piperidin-4-yl]oxy}pyridin-2-yl)-piperazin-1-yl]ethyl} Ethanethioate ***(2i)*** *and S-{2-[4-(3-{[1-(Methylsulfonyl)piperidin-4-yl]oxy}pyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate* ***(2i′)****.* These were obtained as an inseparable mixture, 0.328 g (74% total yield); brown amorphous; R_f = 0.32 ($CHCl_3$/C_2H_5OH = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83−7.87 (m, 1H), 7.10 (dd, *J* = 9.1, 2.9, 0.76H), 7.02 (dd, *J* = 7.8, 1.1 Hz, 0.24H), 6.75 (dd, *J* = 7.8, 4,9 Hz, 0.24H), 6.57 (d, *J* = 9.1 Hz, 0.76H), 4.45−4.51 (m, 0.24H), 4.23−4.39 (m, 0.76H), 3.36−3.43 (m, 4H), 3.19−3.33 (m, 4H), 2.97−3.03, m, 2H), 2.76 (s, 0.72H), 2.74 (s, 2.28H), 2.53−2.65 (m, 6H), 2.27 (s, 3H), 1.83−1.84 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 195.5, 155.4, 153.2, 145.9, 143.5, 140.3, 137.1, 127.6, 123.1, 116.7, 108.0, 72.4, 71.2, 57.5, 57.4, 53.5, 53.0, 52.6, 47.8, 45.9, 42.3, 42.2, 34.8, 34.7, 30.6, 29.89, 29.86, 26.1, 25.9. FT-IR (thin film): ν_{max} (cm^{-1}) 1689 (C═O); 1326, 1158 (SO_2). MS, *m*/*z* (I, %): 442 (M^+, 15), 367 (100), 284 (44), 123 (30). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{31}N_4O_4S_2^+$, 443.1781; found, 443.1785.

S-{2-[4-(5-Propoxypyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate ***(2j)*** *and S-{2-[4-(3-Propoxypyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate* ***(2j′)****.* These were obtained as an inseparable mixture, 0.207 g (64% total yield); brown amorphous; R_f = 0.23 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (d, *J* = 3.0 Hz, 0.84H), 7.84 (dd, *J* = 4.9, 1.5 Hz, 0.16H), 7.13 (dd, *J* = 9.1, 3.0 Hz, 0.84H), 7.00 (dd, *J* = 8.1, 1.5 Hz, 0.16H), 6.79 (dd, *J* = 8.1, 4.9 Hz, 0.16H), 6.61 (d, *J* = 9.1 Hz, 0.84H), 3.86−3.93 (m, 2H), 3.41−3.48 (m, 4H), 3.03−3.09 (m, 2H), 2.57−2.69 (m, 6H), 2.33 (s, 3H), 1.71−1.88 (m, 2H), 0.98−1.07 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.1, 174.1, 154.5, 148.4, 145.9, 138.4, 134.1, 125.3, 118.1, 116.6,

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108.0, 70.4, 69.4, 57.3, 57.1, 52.6, 52.4, 52.3, 45.8, 30.3, 25.6, 22.4, 22.3, 21.4, 10.6, 10.2. FT-IR (thin film): ν_{max} (cm^{-1}) 1692 (C═O). MS, *m*/*z* (I, %): 323 (M^+, 28), 248 (76), 179 (32), 165 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{26}N_3O_2S^+$, 324.1740; found, 324.1742.

*S-{2-[4-(6-Morpholin-4-ylpyridin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2k**).* Yield 0.201 g (57%); dark viscous liquid; R_f = 0.15 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (t, *J* = 8.1 Hz, 1H), 5.99 (d, *J* = 8.1 Hz, 1H), 5.94 (d, *J* = 8.1 Hz, 1H), 3.74−3.77 (m, 4H), 3.46−3.48 (m, 4H), 3.39−3.42 (m, 4H), 3.00−3.03 (m, 2H), 2.53−2.55 (m, 6H), 2.30 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 195.4, 158.3, 158.0, 139.1, 96.3, 95.8, 66.7, 57.2, 52.3, 45.5, 44.5, 30.5, 25.5. FT-IR (thin film): ν_{max} (cm^{-1}) 1697 (C═O). MS, *m*/*z* (I, %): 350 (M^+, 19), 192 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{27}N_4O_2S^+$, 351.1849; found, 351.1847.

*S-{2-[4-(2,2′-Bipyridin-6-yl)piperazin-1-yl]ethyl} Ethanethioate (**2l**).* Yield 0.302 g (88%); yellow viscous liquid; R_f = 0.21 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, *J* = 4.2 Hz, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 7.76−7.79 (m, 2H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.24−7.27 (m, 1H), 6.68−6.70 (d, *J* = 8.3 Hz, 1H), 3.63−3.73 (m, 4H), 3.08−3.12 (m, 2H), 2.62−2.69 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 158.9, 156.9, 154.1, 149.1, 138.6, 136.8, 123.4, 121.1, 110.8, 107.5, 57.6, 52.8, 45.2, 30.7, 26.3. FT-IR (thin film): ν_{max} (cm^{-1}) 1690 (C═O). MS *m*/*z* (I, %): 342 (M^+, 1), 267 (41), 198 (29), 184 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{23}N_4OS^+$, 343.1587; found, 343.1584.

*Ethyl 6-{4-[2-(Acetylthio)ethyl]piperazin-1-yl}pyridine-2-carboxylate (**2m**).* Yield 0.142 g (42%); dark viscous liquid; R_f = 0.27 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53−7.57 (m, 1H), 7.39 (d, *J* = 7.3 Hz, 1H), 6.78 (d, *J* = 8.6 Hz, 1H), 4.37 (q, *J* = 7.1 Hz, 2H), 3.61−3.64 (m, 4H), 3.03−3.07 (m, 2H), 2.57−2.62 (m, 6H), 2.33 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.3, 165.5, 158.5, 164.1, 138.0, 114.6, 110.3, 61.2, 56.9, 52.0, 44.0, 30.4, 25.1, 14.1. FT-IR (thin film): ν_{max} (cm^{-1}) 1740 (C═O), 1678 (C═O). MS, *m*/*z* (I, %): 337 (M^+, 6), 262 (79), 193 (32), 179 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_3S^+$, 338.1533; found, 338.1526.

*Ethyl 2-{4-[2-(Acetylthio)ethyl]piperazin-1-yl}isonicotinate (**2n**).* Yield 0.051 g (15%); amorphous; dark; R_f = 0.27 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.26 (d, *J* = 5.0 Hz, 1H), 7.21 (s, 1H), 7.12 (dd, *J* = 5.0, 1.1 Hz, 1H), 4.37 (q, *J* = 7.1, Hz, 2H), 3.62−3.64 (m, 4H), 3.05−3.09 (m, 2H), 2.61−2.65 (m, 6H), 2.34 (s, 3H), 1.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 165.9, 159.8, 148.8, 139.4, 112.3, 106.9, 61.7, 57.5, 52.6, 44.8, 30.7, 25.9, 14.3. FT-IR (thin film): ν_{max} (cm^{-1}) 1743 (C═O), 1679 (C═O). MS, *m*/*z* (I, %): 337 (M^+, 4), 262 (51), 179 (59). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{24}N_3O_3S^+$, 338.1533; found, 338.1530.

*S-{2-[4-(6-Bromoquinolin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2s**).* Yield 0.371 g (94%); beige solid mp: 139−142 °C; R_f = 0.17 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 9.3 Hz, 1H), 7.65−7.69 (m, 1H), 7.51−7.56 (m, 2H), 6.90 (d, *J* = 9.3 Hz, 1H), 3.69−3.72 (m, 4H), 3.01−3.05 (m, 2H), 2.55−2.59 (m, 6H), 2.32 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6, 157.3, 146.6, 136.4, 132.6, 129.2, 128.4, 124.2, 115.1, 110.2, 57.5, 52.8, 44.9, 30.7, 26.3. FT-IR (KBr): ν_{max} (cm^{-1}) 1685 (C═O). MS, *m*/*z* (I, %): 395, 393 (M^+, 10, 11); 320, 318 (95, 100); 237, 235 (88, 96); 251 (37), 249 (56). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{21}BrN_3OS^+$, 396.0563 and 394.0583; found, 396.0564 and 394.0584.

*S-{2-[4-(5-Chloro-8-methoxyquinolin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2t**).* Yield 0.348 g (92%); light-brown solid; mp: 95−97 °C; R_f = 0.15 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 9.4 Hz, 1H), 7.11 (d, *J* = 8.3 Hz, 1H), 6.97 (d, *J* = 9.4 Hz, 1H), 6.77 (d, *J* = 8.3 Hz, 1H), 3.92 (s, 3H), 3.71−3.74 (m, 4H), 2.99−3.02 (m, 2H), 2.52−2.57 (m, 6H), 2.29 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 156.6, 152.6, 140.0, 134.4, 122.3, 121.6, 121.2, 110.0, 108.5, 57.4, 56.2, 52.7, 44.7, 30.6, 26.2. FT-IR (KBr): ν_{max} (cm^{-1}) 1696 (C═O). MS, *m*/*z* (I, %): 381, 379 (M^+, 1, 3); 223, 221 (30, 100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{23}ClN_3O_2S^+$, 382.1165 and 380.1194; found, 382.1172 and 380.1205.

*S-{2-[4-(4-Cyanoquinolin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2u**).* Yield 0.160 g (47%); yellow solid; mp: 77−80 °C; R_f = 0.40 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.60−7.64 (m, 1H), 7.34−7.37 (m, 1H), 7.29 (s, 1H), 3.74−3.76 (m, 4H), 3.04−3.08 (m, 2H), 2.59−2.64 (m, 6H), 2.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.7, 155.7, 148.0, 131.3, 127.4, 124.6, 124.3, 120.3, 120.2, 116.2, 114.4, 57.5, 52.7, 45.0, 30.7, 26.3. FT-IR (KBr): ν_{max} (cm^{-1}) 2231 (C≡N), 1681 (C═O). MS, *m*/*z* (I, %): 340 (M^+, 2), 265 (100), 222 (40), 196 (83), 116 (94), 158 (41). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_4OS^+$, 341.1431; found, 341.1435.

*Methyl 2-{4-[2-(Acetylthio)ethyl]piperazin-1-yl}quinoline-4-carboxylate (**2v**).* Yield 0.310 g (83%); yellow viscous liquid; R_f = 0.27 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, *J* = 8.5 Hz, 1H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.51 (s, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 4.01 (s, 3H), 3.78−3.83 (m, 4H), 3.07−3.11 (m, 2H), 2.62−2.67 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.8, 167.2, 156.5, 149.0, 136.8, 130.0, 127. 3, 125.4, 123.7, 119.9, 111.7, 57.6, 52.9, 52.7, 45.0, 30.7, 26.3. FT-IR (thin film): ν_{max} (cm^{-1}) 1727 (C═O), 1690 (C═O). MS, *m*/*z* (I, %): 373 (M^+, 1), 298 (71), 229 (42), 215 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{24}N_3O_3S^+$, 374.1533; found, 374.1537.

*S-{2-[4-(6-Chloro-4-methoxyquinolin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2w**).* Yield 0.286 g (75%); brown solid; mp: 89−91 °C; R_f = 0.13 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91 (d, *J* = 2.2 Hz, 1H), 7.55−7.62 (m, 1H), 7.44 (dd, *J* = 8.9, 2.2 Hz, 1H), 6.24 (s, 1H), 4.00 (s, 3H), 3.77−3.83 (m, 4H), 3.08−3.11 (m, 2H), 2.63−2.68 (m, 6H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.4, 162.1, 158.5, 146.7, 130.1, 127.6, 126.6, 120.7, 117.7, 88.0, 57.3, 55.6, 52.2, 44.9, 30.4, 26.0. FT-IR (KBr): ν_{max} (cm^{-1}) 1684 (C═O). MS, *m*/*z* (I, %): 381, 379 (M^+, 2, 6); 306, 304 (26, 83); 223, 221 (31, 100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{23}ClN_3O_2S^+$, 382.1165 and 380.1194; found, 382.1169 and 380.1200.

*S-{2-[4-(1,10-Phenanthrolin-2-yl)piperazin-1-yl]ethyl} Ethanethioate (**2x**).* Yield 0.289 g (79%); brown solid; mp: 77−80 °C; R_f = 0.68 ($CHCl_3/C_2H_5OH$ = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.18−8.20 (m, 1H), 8.25 (d, *J* = 7.4 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.58−7.61 (m, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 3.95−4.01 (m, 4H), 3.11−3.17 (m, 2H), 2.71−2.84 (m, 6H), 2.36 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.5, 157.7, 149.0, 145.1, 144.7, 137.6, 136.3, 129.3, 126.4, 122.13, 122.05, 121.4, 109.5, 57.5, 52.8, 44.7, 30.5, 26.1. FT-IR (KBr): ν_{max} (cm^{-1}) 1687 (C═O). MS, *m*/*z* (I, %): 366 (M^+, 8), 291 (84), 208 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_4OS^+$, 367.1587; found, 367.1591.

*General Procedure for the Synthesis of Compounds **3** (Table 3, General Procedure C).* Compounds **3** were prepared using general procedure B with the following alterations: (a) for the compounds **3a**−**3s**, various sulfur-based nucleophiles were employed instead of thioacetic acid; the reaction mixture was stirred overnight at rt (or at 90 °C for compound **3s**) after addition of a nucleophile; (b) for compounds **3q** and **3r**, K_2CO_3 (2.76 g, 20 mmol, 5 equiv) was added, and the reaction mixture was stirred for 30 min before addition of a nucleophile; the corresponding sodium salts prepared from SH-compounds and NaH were employed as nucleophiles.

*2-{4-[2-(Phenylthio)ethyl]piperazin-1-yl}quinoline (**3a**).* Thiophenol (440 mg) was employed; yield 0.300 g (86%); off-white solid; mp: 91−93 °C; R_f = 0.70 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 9.1 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.52−7.56 (m, 1H), 7.38 (d, *J* = 7.3 Hz, 2H), 7.28−7.32 (m, 2H), 7.17−7.35 (m, 2H), 7.94 (d, *J* = 9.1 Hz, 1H), 3.74−3.77 (m, 4H), 3.09−3.13 (m, 2H), 2.68−2.72 (m, 2H), 2.60−2.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 147.9, 137.5, 136.4, 129.6, 129.1, 129.0, 127.2, 126.7, 126.0, 123.1, 122.4, 109.5, 57.8, 53.0, 45.0, 30.8. MS, *m*/*z* (I, %): 349 (M^+, 6) 240 (100), 171 (51), 157 (91), 128 (36). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{24}N_3S^+$, 350.1685; found, 350.1691.

*6-Bromo-2-{4-[2-(phenylthio)ethyl]piperazin-1-yl}quinoline (**3b**).* Thiophenol (440 mg) was employed; yield 0.381 g (89%); yellow

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solid; mp: 103−106 °C; R_f = 0.73 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 9.3 Hz, 1H), 7.71−7.72 (m, 1H), 7.53−7.59 (m, 2H), 7.37 (d, J = 8.1 Hz, 2H), 7.27−7.31 (m, 2H), 7.17−7.20 (m, 1H), 6.96 (d, J = 9.3 Hz, 1H), 3.73−3.76 (m, 4H), 3.09−3.12 (m, 2H), 2.68−2.71 (m, 2H), 2.59−2.62 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 146.7, 136.5, 136.4, 132.8, 129.3, 129.1, 128.5, 126.2, 124.3, 115.2, 110.3, 57.8, 53.1, 45.0, 31.0. MS, *m*/*z* (I, %): 429, 427 (M^+, 6, 6); 320, 318 (98, 100); 251, 249 (56, 69); 306, 304 (47, 48); 237, 235 (43, 46). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{23}BrN_3S^+$, 430.0770 and 428.0791; found, 430.0772 and 428.0793.

5-Chloro-8-methoxy-2-{4-[2-(phenylthio)ethyl]piperazin-1-yl}-quinoline (**3c**). Thiophenol (440 mg) was employed; yield 0.335 g (81%); yellow solid; mp: 105−108 °C; R_f = 0.51 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, J = 9.5 Hz, 1H), 7.51 (d, J = 7.3 Hz, 1H), 7.39 (d, J = 7.3, 2H), 7.30−7.33 (m, 2H), 7.23−7.24 (m, 1H), 7.07 (d, J = 9.3 Hz, 1H), 6,86 (d, J = 8.6 Hz, 1H), 4.01 (s, 3H), 3.80−3.90 (m, 4H), 3.13−3.20 (m, 2H), 2.64−2.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.6, 152.6, 140.0, 136.3, 134.4, 129.0, 128.9, 125.9, 122.3, 121.6, 121.2, 110.0, 108.5, 57.6, 56.1, 52.9, 44.7, 30.7. MS, *m*/*z* (I, %): 415, 413 (M^+, 2, 4); 306, 304 (33, 100); 223, 221 (19, 60). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{25}ClN_3OS^+$, 416.1372 and 414.1401; found, 414.1403 and 416.1377.

2-{4-[2-(Phenylthio)ethyl]piperazin-1-yl}-1,10-phenanthroline (**3d**). Thiophenol (440 mg) was employed; yield 0.293 g (73%); yellow solid; mp: 130−133 °C; R_f = 0.45 ($CHCl_3/C_2H_5OH$ = 10/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.12−9.13 (m, 1H), 8.20 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 8.9 Hz, 1H), 7.65 (d, J = 8.7 Hz, 1H), 7.54−7.56 (m, 1H), 7.51 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H), 7.31 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 8.9 Hz, 1H), 3.95−4.05 (m, 4H), 3.16−3.23 (m, 2H), 2.71−2.81 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5, 149.0, 145.1, 144.9, 137.4, 136.1, 135.7, 129.1, 128.70, 128.65, 126.1, 125.7, 121.9, 121.8, 121.3, 109.1, 57.4, 52.7, 44.6, 30.4. MS, *m*/*z* (I, %): 400 (M^+, 1), 240 (100), 226 (44), 171 (45), 157 (87). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{25}N_4S^+$, 401.1794; found, 401.1789.

1-(5-Phenylpyridin-2-yl)-4-[2-(phenylthio)ethyl]piperazine (**3e**). Thiophenol (440 mg) was employed; yield 0.294 g (78%); white solid; mp: 82−85 °C; R_f = 0.72 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (d, J = 2.2 Hz, 1H), 7.74 (dd, J = 8.8, 2.2 Hz, 1H), 7.51−7.55 (m, 2H), 7.37−7.46 (m, 4H), 7.30−7.33 (m, 3H), 7.19−7.23 (m, 1H), 6.73 (d, J = 8.8 Hz, 1H), 3.63−3.72 (m, 4H), 3.14−3.20 (m, 2H), 2.66−2.79 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.3, 145.9, 138.0, 136.2, 135.8, 128.8, 128.7, 126.5, 125.9, 125.8, 57.4, 52.5, 44.8, 30.4. MS, *m*/*z* (I, %): 375 (M^+, 13), 266 (100), 252 (81), 223 (34), 197 (60), 183 (65). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{26}N_3S^+$, 376.1842; found, 376.1840.

2-(4-{2-[(4-Methylphenyl)thio]ethyl}piperazin-1-yl)quinoline (**3f**). 4-Methylthiophenol (497 mg) was employed; yield 0.305 g (84%); white solid; mp: 100−102 °C; R_f = 0.76 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 9.1, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.55−7.62 (m, 2H), 7.34 (d. J = 8.1 Hz, 2H), 7.24−7.27 (m, 1H), 7.14 (d, J = 8.1 Hz, 2H), 6.93 (d, J = 9.1 Hz, 1H), 3.75−3.77 (m, 4H), 3.06−3.10 (m, 2H), 2.67−2.71 (m, 2H), 2.58−2.60 (m, 4H), 2.35 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.2, 147.8, 137.3, 136.0, 132.4, 129.8, 129.6, 129.4, 127.1, 126.6, 123.0, 122.3, 109.4, 57.7, 52.4, 52.8, 44.8, 31.3, 20.9. MS, *m*/*z* (I, %): 363 (M^+, 7), 240 (100), 226 (44), 171 (45), 157 (87). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{26}N_3S^+$, 364.1842; found, 364.1840.

2-(4-{2-[(4-Chlorophenyl)thio]ethyl}piperazin-1-yl)quinoline (**3g**). 4-Chlorothiophenol (578 mg) was employed; yield 0.292 g (76%); off-white solid; mp: 109−111 °C; R_f = 0.68 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 9.1 Hz, 1H), 7.70−7.73 (m, 1H), 7.60 (d, J = 7.8 Hz, 1H), 7.52−7.56 (m, 1H), 7.22−7.32 (m, 5H), 6.97 (d, J = 9.1 Hz, 1H), 3.77−3.85 (m, 4H), 3.09−3.13 (m, 2H), 2.65−2.72 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 147.8, 137.4, 134.9, 131.9, 130.4, 129.5, 129.0, 127.2, 126.6, 123.1, 122.4, 109.5, 57.5, 52.9, 44.9, 31.1. MS, *m*/*z* (I, %): 385, 383 (M^+, 2, 5); 240 (72), 171 (42), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{23}ClN_3S^+$, 386.1266 and 384.1296; found, 386.1263 and 384.1290.

6-Bromo-2-(4-{2-[(4-chlorophenyl)thio]ethyl}piperazin-1-yl)-quinoline (**3h**). 4-Chlorothiophenol (578 mg) was employed; yield 0.329 g (71%); light-brown solid; mp: 90−93 °C; R_f = 0.73 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 9.1 Hz, 1H), 7.73 (s, 1H), 7.54−7.62 (m, 2H), 7.26−7.32 (m, 4H), 6.97 (d, J = 9.0 Hz, 1H), 3.75−3.83 (m, 4H), 3.08−3.17 (m, 2H), 2.60−2.76 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 146.6, 136.3, 134.9, 132.5, 131.8, 130.3, 129.1, 128.9, 128.3, 124.1, 115.0, 110.1, 57.3, 52.8, 44.7, 31.0. MS, *m*/*z* (I, %): 465, 463, 461 (M^+, 7, 8, 7); 320, 318 (100, 98). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}BrClN_3S^+$, 466.0351, 464.0380, and 462.0401; found, 466.0361, 464.0385, and 462.0407.

(2-{[2-(4-Quinolin-2-ylpiperazin-1-yl)ethyl]thio}phenyl)amine (**3i**). 2-Aminothiophenol (500 mg) was employed; yield 0.270 g (74%); off-white solid; mp: 88−91 °C; R_f = 0.35 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 9.1 Hz, 1H), 7.70 (d, J = 8.3 Hz, 1H), 7.59 (dd, J = 8.0, 0.8 Hz, 1H), 7.53 (t, J = 7.0 Hz, 1H), 7.41 (dd, J = 7.7, 1.5 Hz, 1H), 7.22 (t, J = 7.0 Hz, 1H), 7.12 (t, J = 7.7 Hz, 1H), 6.96 (d, J = 9.1 Hz, 1H), 6.67−6.73 (m, 2H), 4.49 (br, 2H), 3.73−3.75 (m, 4H), 2.90−2.94 (m, 2H), 2.57−2.63 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.0, 148.6, 147.5, 137.1, 135.8, 129.5, 129.2, 127.0, 126.3, 122.8, 122.1, 117.9, 117.0, 114.6, 109.3, 57.3, 52.4, 44.7, 31.8. FT-IR (KBr): ν_{max} (cm^{-1}) 3423, 3324 (NH_2); 1234 (C − N). MS, *m*/*z* (I, %): 364 (M^+, 8); 240 (100), 171 (43), 157 (54). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{25}N_4S^+$, 365.1794; found, 365.1798.

2-{4-[2-(Pyridin-2-ylthio)ethyl]piperazin-1-yl}quinoline (**3j**). 2-Mercaptopyridine (445 mg) was employed; yield 0.277 g (79%); yellow solid, mp: 79−82 °C; R_f = 0.38 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (d, J = 4.0 Hz, 1H), 7.85 (d, J = 9.1 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.50−7.53 (m, 1H), 7.42−7.45 (m, 1H), 7.16−7.22 (m, 2H), 6.94 (d, J = 9.1 Hz, 2H), 3.75−3.79 (m, 4H), 3.36−3.40 (m, 2H), 2.67−2.78 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 157.3, 149.5, 147.8, 137.5, 135.9, 129.5, 127.2, 126.6, 123.1, 122.3, 119.4, 109.5, 57.9, 52.9, 45.0, 26.9. MS, *m*/*z* (I, %): 350 (M^+, 2), 240 (86), 171 (37), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{20}H_{23}N_4S^+$, 351.1638; found, 351.1643.

2-{4-[2-(1,3-Benzothiazol-2-ylthio)ethyl]piperazin-1-yl}quinoline (**3k**). 2-Mercaptobenzothiazol (669 mg) was employed; yield 0.241 g (59%); white solid; mp: 103−105 °C; R_f = 0.71 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87−7.90 (m, 2H), 7.73−7.76 (m, 2H), 7.53−7.61 (m, 2H), 7.41−7.44 (m, 1H), 7.22−7.32 (m, 2H), 6.95−6.97 (m, 1H), 3.76−3.38 (m, 4H), 3.56−3.60 (m, 2H), 2.86−2.89 (m, 2H), 2.67−2.69 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 157.3, 153.3, 147.9, 137.5, 135.3, 129.6, 127.3, 126.7, 126.1, 124.3, 123.1, 122.5, 121.5, 121.1, 109.6, 57.2, 52.9, 45.1, 30.9. MS, *m*/*z* (I, %): 406 (M^+, 8), 240 (63), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{23}N_4S_2^+$, 407.1359; found, 407.1359

2-{4-[2-(1,3-Benzothiazol-2-ylthio)ethyl]piperazin-1-yl}-6-bromo-quinoline (**3l**). 2-Mercaptobenzothiazol (669 mg) was employed; yield 0.306 g (63%); off-white solid; mp: 106−109 °C; R_f = 0.75 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 8.1 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.74−7.77 (m, 2H), 7.54−7.61 (m, 2H), 7.42 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 6.98 (d, J = 9.2 Hz, 1H), 3.55−4.00 (m, 6H), 2.65−3.03 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 157.3, 153.3, 146.6, 136.5, 135.3, 132.7, 129.2, 128.4, 126.1, 124.3, 124.2, 121.5, 121.1, 115.1, 110.3, 57.1, 52.9, 44.9, 30.9. MS, *m*/*z* (I, %): 486, 484 (M^+, 34, 30); 320, 318 (78, 80); 237, 235 (100, 99). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{22}BrN_4S_2^+$, 487.0443 and 485.0464; found, 487.0442 and 485.0463.

2-({2-[4-(5-Phenylpyridin-2-yl)piperazin-1-yl]ethyl}thio)-1,3-benzothiazole (**3m**). 2-Mercaptobenzothiazol (669 mg) was employed; yield 0.217 g (50%); off-white solid; mp: 110−113 °C; R_f = 0.72 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.45 (d, J = 2.1 Hz, 1H), 7.86 (d, J = 8.2 Hz, 1H), 7.72−7.77 (m, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.40−7.44 (m, 3H), 7.28−7.33 (m, 2H), 6.73 (d, J = 8.8 Hz, 1H), 3.58−3.72 (m, 6H), 2.67−3.00 (m, 6H). ^{13}C NMR (100

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MHz, $CDCl_3$): δ 167.0, 158.6, 153.3, 146.2, 138.4, 136.2, 135.3, 129.0, 126.8, 126.3, 126.2, 126.1, 124.3, 121.5, 121.1, 106.9, 57.1, 52.8, 45.2, 30.8. MS, *m*/*z* (I, %): 432 (M^+, 41), 266 (63), 265 (38), 197 (50), 183 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{24}H_{25}N_4S_2^+$, 433.1515; found, 433.1518.

2-{4-[2-(1,3,4-Thiadiazol-2-ylthio)ethyl]piperazin-1-yl}quinoline (**3n**). 2-Mercapto-1,3.4-thiadiazol (472 mg) was employed; yield 0.275 g (77%); yellow solid; mp: 88−91 °C; R_f = 0.43 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.99 (s, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 8.3 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.51−7.55 (m, 1H), 7.20−7.24 (m, 1H), 6.96 (d, *J* = 9.2 Hz, 1H), 3.74−3.77 (m, 4H), 3.59−3.63 (m, 2H), 2.86−2.89 (m, 2H), 2.66−2.68 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 157.1, 151.3, 147.6, 137.3, 129.4, 127.1, 126.4, 122.9, 122.3, 109.4, 56.5, 52.6, 44.8, 31.5. MS, *m*/*z* (I, %): 357 (M^+, 10), 240 (57), 171 (30), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{17}H_{20}N_5S_2^+$, 358.1155; found, 358.1147.

6-Chloro-4-methoxy-2-{4-[2-(1,3,4-thiadiazol-2-ylthio)ethyl]-piperazin-1-yl}quinoline (**3o**). 2-Mercapto-1,3,4-thiadiazol (472 mg) was employed; yield 0.232 g (55%); light-yellow solid; mp: 74−77 °C; R_f = 0.19 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 7.84 (s, 1H), 7.52 (d, *J* = 8.9 Hz, 1H), 7.37 (d, *J* = 8.9 Hz, 1H), 6.17 (s, 1H), 3.91 (s, 3H), 3.66−3.70 (m, 4H), 3.53−3.56 (m, 2H), 2.81−2.84 (m, 2H), 2.60−2.64 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 162.4, 158.6, 151.4, 146.8, 130.4, 127.6, 127.0, 120.9, 117.9, 88.2, 56.7, 55.4, 52.7, 45.1, 31.5. MS, *m*/*z* (I, %): 423, 421 (M^+, 1, 2); 223, 221 (100, 33). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{21}ClN_5OS_2^+$, 424.0841 and 422.0871; found, 424.0835 and 422.0867.

2-[4-(2-{[5-(2-Furyl)-1,3,4-oxadiazol-2-yl]thio}ethyl)piperazin-1-yl]quinoline (**3p**). 2-Mercapto-5-(2-furyl)-1,3.4-oxadiazol (672 mg) was employed; yield 0.213 g (52%); light-brown solid; mp 77−80 °C; R_f = 0.19 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 8.6 Hz, 1H), 7.57−7.61 (m, 2H), 7.51−7.54 (m, 1H), 7.20−7.23 (m, 1H), 7.10 (d, *J* = 3.4 Hz, 1H), 6.95 (d, *J* = 9.1 Hz, 1H), 6.56−6.57 (m, 1H), 3.73−3.75 (m, 4H), 3.49−3.52 (m, 2H), 2.84−2.88 (m, 2H), 2.64−2.67 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 158.1, 156.9, 147.5, 145.4, 138.7, 137.1, 129.2, 127.0, 126.3, 122.8, 122.1, 113.6, 111.9, 109.3, 56.2, 52.4, 44.7, 30.2. MS, *m*/*z* (I, %): 407 (M^+, 10), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{22}N_5O_2S^+$, 408.1489; found, 408.1492.

6-Bromo-2-{4-[2-(4,5-dihydro-1,3-thiazol-2-ylthio)ethyl]-piperazin-1-yl}quinoline (**3q**). A solution of sodium 4,5-dihydro-1,3-thiazole-2-thiolate, prepared from 4,5-dihydro-1,3-thiazole-2-thiol (477 mg, 4 mmol) and NaH (60% w/w suspension, 160 mg, 4 mmol) in 5 mL of DMF, was used; yield 0.214 g (49%); light-yellow solid; mp 83−86 °C; R_f = 0.32 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (d, *J* = 9.1 Hz, 1H), 7.69 (s, 1H), 7.50−7.57 (m, 2H), 6.93 (d, *J* = 9.3 Hz, 1H), 4.19 (t, *J* = 7.8 Hz, 2H), 3.70−3.75 (m, 4H), 3.37 (t, *J* = 7.8 Hz, 2H), 3.25−3.30 (m, 2H), 2.71−2.41 (m, 2H), 2.58−2.65 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.5, 157.4, 146.6, 136.5, 132.7, 129.2, 128.4, 124.2, 115.1, 110.4, 110.3, 64.3, 57.2, 52.8, 44.9, 35.6, 30.0. MS, *m*/*z* (I, %): 438, 436 (M^+, 20, 19); 319, 317 (100, 97); 237, 235 (87, 87). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{18}H_{22}BrN_4S_2^+$, 439.0443 and 437.0464; found, 439.0440 and 437.0461.

1-{2-[(4-Methoxybenzyl)thio]ethyl}-4-(5-phenylpyridin-2-yl)-piperazine (**3r**). A solution of sodium 4-methoxybenzyithiolate, prepared from 4-methoxybenzylmercaptan (616 mg, 4 mmol) and NaH (60% w/w suspension, 160 mg, 4 mmol) in 5 mL of DMF, was used; yield 0.317 g (76%); white; mp 96−99 °C; R_f = 0.54 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (d, *J* = 2.5 Hz, 1H), 7.72 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.24−7.27 (m, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 2H), 3.59−3.69 (m, 4H), 2.58−2.68 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 158.5, 146.0, 138.2, 136.0, 130.4, 130.2, 129.9, 128.8, 126.7, 126.1, 113.8, 106.7, 58.1, 55.2, 52.7, 45.0, 35.9, 28.1. MS, *m*/*z* (I, %): 419 (M^+, 6), 266 (100), 252 (96), 223 (34), 197 (62), 183 (62). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{25}H_{30}N_3OS^+$, 420.2104; found, 420.2101.

2-(4-{2-[(4-Methylphenyl)sulfonyl]ethyl}piperazin-1-yl)quinoline (**3s**). Sodium *p*-toluenesulfinate (714 mg) was employed; yield 0.088 g (22%); off-white amorphous; R_f = 0.42 (EtOAc/*n*-hexane = 2/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, *J* = 9.1, 1H), 7.81 (d, *J* = 8.2, 2H), 7.68 (d, *J* = 8.6, 1H), 7.58 (d, *J* = 8.1, 1H), 7.50−7.54 (m, 1H), 7.35 (d, *J* = 8.2, 2H), 7.20−7.24 (m, 1H), 6.92 (d, *J* = 9.1, 1H), 3.61−3.63 (m, 4H), 3.32−3.35 (m, 2H), 2.81−2.84 (m, 2H), 2.49−2.51 (m, 4H), 2.44 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 144.9, 141.1, 137.9, 136.8, 130.0, 129.9, 128.2, 127.4, 126.4, 123.1, 122.8, 109.6, 53.7, 52.8, 45.1, 21.8. FT-IR (KBr): ν_{max} (cm^{-1}): 1330, 1145 (SO_2). MS, *m*/*z* (I, %): 395 (M^+, 4), 157 (100), 240 (70), 139 (37). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{22}H_{26}N_3O_2S^+$, 396.1740; found, 396.1740.

1-{2-[4-(6-Bromoquinolin-2-yl)piperazin-1-yl]ethyl}-4-aza-1-azoniabicyclo[2.2.2]octane Thiocyanate (**4a**). General procedure B was used with the following alterations: (a) sodium thiocyanate (324 mg, 4 mmol, 4 equiv) was employed, and the resulting mixture was stirred at 90 °C overnight; (b) after solvent evaporation at the end of the reaction, the residue was diluted with water (20 mL), the resulting solution was kept at 0−4 °C overnight, and the precipitated solid was filtered, washed with cold water, and dried under reduced pressure. Yield 0.450 g (92%); white solid; mp 190−193 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 8.00−8.01 (d, *J* = 9.1 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.59 (dd, *J* = 8.8, 2.0, 1H), 7.47 (d, *J* = 8.8, 1H), 7.29−7.30 (d, *J* = 9.1 Hz, 1H), 3.68−3.72 (m, 4H), 3.37−3.52 (m, 8H), 3.04−3.06 (m, 6H), 2.78−2.79 (m, 2H), 2.57−2.59 (m, 4H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 157.2, 146.0, 136.6, 132.2, 129.6, 129.3, 128.1, 124.2, 114.0, 111.2, 59.5, 52.3, 52.2, 50.3, 44.8, 44.4. FT-IR (KBr): ν_{max} (cm^{-1}) 2055 (SC≡N). HRMS (ESI) *m*/*z*: $[M - SCN]^+$ calcd for $C_{21}H_{29}N_5Br^+$, 432.1580 and 430.1601; found, 432.1581 and 430.1603.

General Procedure for the Synthesis of Compounds **5** *(Table 4, General Procedure D).* Compounds **5** were prepared using general procedure B with the following alterations: (a) DMF was used as the solvent in all examples; (b) the reaction mixture was stirred at 90 °C for 8 h prior to addition of a nucleophile; and (c) after addition of a nucleophile, the resulting mixture was stirred at 90 °C overnight.

S-(2-{4-[2-(4-Quinolin-2-ylpiperazin-1-yl)ethyl]piperazin-1-yl}-ethyl) Ethanethioate (**5a**). This was synthesized using thioacetic acid (304 mg) as the nucleophile; yield 0.355 g (83%); also was prepared following the general procedure from 2 g (13.8 mmol) of **1a** in yield 85% (5.01 g); amorphous; light-brown; R_f = 0.51 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.88 (d, *J* = 9.1 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.52 (t, *J* = 7.1 Hz, 1H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 9.1 Hz, 1H), 3.74−3.77 (m, 4H), 3.00−3.03 (m, 2H), 2.53−2.66 (m, 18H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.2, 157.1, 147.6, 137.1, 129.2, 126.9, 126.4, 122.8, 122.1, 109.3, 57.1, 55.7, 55.6, 53.3, 53.2, 52.5, 44.8, 30.4, 26.1. FT-IR (KBr): ν_{max} (cm^{-1}) 1690 (C═O). MS, *m*/*z* (I, %): 427 (M^+, 14), 226 (85), 201 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{34}N_5OS^+$, 428.2479; found, 428.2485.

6-Bromo-2-{4-[2-{4-[2-(phenylthio)ethyl]piperazin-1-yl}ethyl)-piperazin-1-yl]quinoline (**5b**). This was synthesized using thiophenol (440 mg); yield 0.411 g (76%); amorphous; off-white; R_f = 0.59 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.77 (d, *J* = 9.1 Hz, 1H), 7.71 (d, *J* = 1.5 Hz, 1H), 7.53−7.58 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.26−7.34 (m, 2H), 7.16−7.18 (m, 1H), 6.96 (d, *J* = 9.1 Hz, 1H), 3.73−3.75 (m, 4H), 3.03−3.06 (m, 4H), 2.87−2.89 (m, 4H), 2.56−2.63 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 146.7, 136.5, 136.4, 132.7, 129.3, 129.1, 129.0, 128.4, 126.0, 124.3, 115.2, 110.3, 57.7, 56.0, 55.9, 53.6, 53.1, 45.0, 30.8. MS, *m*/*z* (I, %): 539, 541 (M^+, 4, 4); 235 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{27}H_{35}BrN_5S^+$, 542.1771 and 540.1791; found, 542.1766 and 540.1787.

6-Bromo-2-{4-[2-(4-{2-[(4-methoxybenzyl)thio]ethyl}piperazin-1-yl)ethyl]piperazin-1-yl}quinoline (**5c**). This was synthesized using sodium 4-methoxybenzyithiolate, prepared from 4-methoxybenzylmercaptan (616 mg, 4 mmol) and NaH (60% w/w suspension, 160 mg, 4 mmol) in 5 mL of DMF; yield 0.461 g (79%); yellow solid; mp: 55−58 °C, R_f = 0.56 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (600 MHz,

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$CDCl_3$): δ 7.77 (d, J = 9.1 Hz, 1H), 7.71 (d, J = 1.5 Hz, 1H), 7.53−7.56 (m, 2H), 7.22 (d, J = 8.6, 2H), 6.96 (d, J = 9.1 Hz, 1H), 6.83 (d, J = 8.6, 2H), 3.79 (s, 3H), 3.72−3.76 (m, 4H), 3.68 (s, 2H), 2.42−2.61 (m, 20H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 157.4, 146.6, 136.5, 132.7, 130.3, 129.9, 129.2, 128.3, 124.2, 115.1, 113.9, 110.3, 58.01, 55.8, 55.7, 55.3, 53.5, 53.4, 52.8, 44.9, 35.9, 28.1. MS, *m*/*z* (I, %): 585, 583 (M^+, 1, 2), 279 (65), 121 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{29}H_{39}BrN_5OS^+$, 586.2033 and 584.2053; found, 586.2031 and 584.2050.

*2-(4-{2-[4-(2-Azidoethyl)piperazin-1-yl]ethyl}piperazin-1-yl)-quinoline (**5d**).* This was synthesized using sodium azide (260 mg); yield 0.240 g (61%); amorphous; yellow; R_f = 0.38 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.89 (d, J = 9.1 Hz, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.52−7.54 (m, 1H), 7.21−7.23 (m, 1H), 6.97 (d, J = 9.1 Hz, 1H), 3.74−3.78 (m, 4H), 3.34−3.36 (m, 2H), 2.51−2.72 (m, 18H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 157.4, 147.9, 137.6, 129.7, 127.3, 126.7, 123.1, 122.6, 109.6, 57.1, 55.42, 55.39, 53.54, 53.49, 52.6, 48.2, 45.1. FT-IR (KBr): ν_{max} (cm^{-1}) 2104, 2066 (N_3). MS, *m*/*z* (I, %): 394 (M^+, 5), 226 (100), 171 (50), 157 (58), 128 (49). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{31}N_8^+$, 395.2666; found, 395.2670.

*Reactions of Salt **A** with Nucleophiles (Table 5, General Procedure E).* To a solution of quinoline *N*-oxide **1a** (145 mg, 1 mmol, 1 equiv) or 6-bromoquinoline *N*-oxide **1s** (224 mg) in DMF (20 mL, 0.05 M) was added 1,4-diazabicyclo[2.2.2]octane (DABCO, 784 mg, 7 mmol, 7 equiv) in one portion. To the mixture cooled to 0 °C was added trifluoroacetic anhydride (525 mg, 350 μL, 2.5 mmol, 2.5 equiv) dropwise. The resulted mixture was stirred for 1 h at rt. A solution of a nucleophilic reagent (4 mmol, 4 equiv) in DMF (5 mL) was slowly added, and the resulted mixture was stirred at 60 °C overnight. The solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of CH_2Cl_2 and was washed with a saturated solution of $NaHCO_3$ (3 × 20 mL), water layers were combined and extracted CH_2Cl_2 (4 × 20 mL), all organic layers were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel using gradient mixtures of EtOAc−*n*-hexane (1:4 to 1:0) or CH_2Cl_2−MeOH (20:1 to 2:1) as eluent.

*2-[2-(4-Quinolin-2-ylpiperazin-1-yl)ethyl]-1H-isoindole-1,3(2H)-dione (**6a**).* This was synthesized from *N*-oxide **1a** and potassium phthalimide (740 mg); yield 0.208 g (54%); white solid; mp: 145−147 °C; R_f = 0.58 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83−7.88 (m, 3H), 7.68−7.73 (m, 3H), 7.58 (d, J = 7.8, 1H), 7.50−7.54 (m, 1H), 7.19−7.23 (m, 1H), 6.94−6.97 (d, J = 9.2, 1H), 3.87−3.90 (m, 2H), 3.67−3.71 (m, 4H), 2.67−2.73 (m, 6H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 167.6, 156.9, 147.1, 137.0, 134.1, 131.5, 129.1, 127.1, 126.9, 122.8, 122.6, 121.8, 109.8, 54.9, 52.3, 44.5, 34.9. FT-IR (KBr): ν_{max} (cm^{-1}) 1712 (C═O). MS, *m*/*z* (I, %): 386 (M^+, 7), 242 (37), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{23}N_4O_2^+$, 387.1816; found, 387.1818.

*2-{4-[2-(1-Methylhydrazino)ethyl]piperazin-1-yl}quinoline (**6b**).* This was synthesized from *N*-oxide **1a** and methylhydrazine (184 mg); yield 0.214 g (75%); amorphous; yellow; R_f = 0.54 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, J = 9.1 Hz, 1H), 7.68 (d, J = 8.3 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.49−7.53 (m, 1H), 7.18−7.22 (m, 1H), 6.95 (d, J = 9.1 Hz, 1H), 3.73−3.76 (m, 4H), 2.98 (s, 3H), 2.56−2.63 (m, 6H), 2.47−2.50 (m, 2H), 1.94 (br, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 147.9, 137.5, 129.6, 127.3, 126.7, 123.2, 122.5, 109.6, 55.9, 53.5. 45.2, 39.3, 15.2. FT-IR (KBr): ν_{max} (cm^{-1}) 3255 (NH_2). MS, *m*/*z* (I, %): 285 (M^+, 18), 226 (100), 200 (55), 197 (48), 171 (89), 157 (58), 128 (55). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{24}N_5^+$, 286.2026; found, 286.2016.

*6-Bromo-2-[4-(2-morpholin-4-ylethyl)piperazin-1-yl]quinoline (**6c**).* This was synthesized from *N*-oxide **1s** and morpholine (348 mg); yield 0.340 g (84%); yellow solid; mp: 113−116 °C; R_f = 0.41 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74−7.77 (d, J = 9.3 Hz, 1H), 7.70 (s, 1H), 7.52−7.57 (m, 2H), 6.93−6.96 (d, J = 9.1 Hz, 1H), 3.64−3.77 (m, 8H), 2.61−2.64 (m, 4H), 2.56−2.60 (m, 4H), 2.50−2.52 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 146.7, 136.5, 132.7, 129.3, 128.4, 124.3, 115.2, 110.3, 66.9, 56.3, 55.6, 54.2, 53.6, 44.9. MS, *m*/*z* (I, %): 406, 404 (M^+, 3, 4), 306, 304 (89, 92); 251, 249 (39, 46); 100 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{26}BrN_4O^+$, 407.1264 and 405.1285; found, 407.1265 and 405.1286.

*3-(4-Quinolin-2-ylpiperazin-1-yl)propanenitrile (**6d**).* This was synthesized from *N*-oxide **1a** and sodium cyanide (196 mg); yield 0.166g (62%); brown solid; mp: 68−70 °C; R_f = 0.42 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.90 (d, J = 9.1 Hz, 1H), 7.71 (d, J = 8.2 Hz, 1H), 7.60 (d, J = 8.2 Hz, 1H), 7.52−7.56 (m, 1H), 7.21−7.25 (m, 1H), 6.97 (d, J = 9.1 Hz, 1H), 3.76−3.79 (m, 4H), 2.74−2.78 (m, 2H), 2.63−2.67 (m, 4H), 2.57−2.59 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3, 147.8, 137.6, 129.6, 127.3, 126.6, 123.1, 122.5, 118.8, 109.5, 53.4, 52.6, 45.0, 15.9. FT-IR (KBr): ν_{max} (cm^{-1}) 2248 (C≡N). MS, *m*/*z* (I, %): 266 (M^+, 11), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{19}N_4^+$, 267.1604; found, 267.1605.

*2-[4-(2-Azidoethyl)piperazin-1-yl]quinoline (**6e**) and Tetrazolo-[1,5-a]quinoline (**7e**).* These were obtained from *N*-oxide **1a** (170 mg, 1.17 mmol) and sodium azide (292 mg) as an inseparable solid mixture (1:1 molar ratio), yield 0.237 g. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 8.4 Hz, 1H), 7.95−8.00 (m, 2H), 7.86−7.92 (m, 3H), 7.71−7.79 (m, 2H), 7.60 (d, J = 8.1 Hz, 1H), 7.53−7.56 (m, 1H), 7.22−7.26 (m, 1H), 6,98 (d, J = 9.2 Hz, 1H), 3.79−3.86 (m, 4H), 3.44−3.47 (m, 2H), 2,69−2.73 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 147.2, 137.6, 133.3, 131.0, 130.5, 129.5, 128.9, 127.9, 127.1, 126.2, 123.6, 122.9, 122.4, 116.5, 112.3, 109.4, 56.9, 52.8, 47.8, 44.8. FT-IR (KBr): ν_{max} (cm^{-1}) 2105, 2060 (N_3). MS, *m*/*z* (I, %): 282 (**6e**: M^+, 7), 170 (**7e**: M^+, 18), 240 (49), 157 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{19}N_6^+$, 283.1666; found, 283.1666; calcd for $C_9H_7N_4^+$, 171.0665; found, 171.0666.

*6-Bromo-2-(4-fluorophenoxy)quinoline (**7f**).* This was synthesized from *N*-oxide **1s** and sodium 4-fluorophenolate prepared from 4-fluorophenol (448 mg) and NaH (60% w/w suspension, 160 mg, 4 mmol) in 5 mL of DMF; yield 0.054 g (19%); off-white solid; mp 91−94 °C; R_f = 0.82 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (d, J = 8.9 Hz, 1H), 7.90 (d, J = 2.0 Hz, 1H), 5.67 (dd, J = 8.9, 2.2, 1H), 7.61 (d, J = 8.9 Hz, 1H), 7.09−7.22 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4 (J_{CF} = 245.5 Hz), 159.0, 149.3 (J_{CF} = 2.0 Hz), 145.0, 138.9, 133.2, 129.6, 129.5, 124.4, 123.2 (J_{CF} = 8.3 Hz), 118.4, 116.2 (J_{CF} = 23.2 Hz), 113.7. MS, *m*/*z* (I, %): 318, 316 (M^+, 78, 70); 127 (100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{10}BrFNO^+$, 319.9904 and 317.9924; found, 319.9903 and 317.9929.

*S-(2-{4-[5,7-Dichloro-4-(4-fluorophenoxy)quinolin-2-yl]piperazin-1-yl}ethyl) Ethanethioate (**8**, Scheme 4A).* This was prepared from quinoxyfen *N*-oxide[55] (324 mg). General procedure B was used with the following alterations: (a) After the end of the reaction, the solvent was removed under reduced pressure, and the residue was dissolved in 20 mL of CH_2Cl_2 and was washed with saturated $NaHCO_3$ aq solution (3 × 20 mL), water layers were combined and extracted with CH_2Cl_2 (2 × 10 mL), all organic layers were combined and washed with a 10% solution of citric acid (4 × 20 mL), water layers were combined and neutralized with 15% NaOH aq solution, extracted with EtOAc (3 × 20 mL), organic layers was combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. Yield 0.335 g (68%); yellow amorphous; R_f = 0.13 (EtOAc/*n*-hexane = 1/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 2.0 Hz, 1H), 7.10−7.13 (m, 2H), 7.05−7.07 (m, 2H), 6.12 (s, 1H), 3.59−3.61 (m, 4H), 3.02−3.05 (m, 2H), 2,59−2.62 (m, 6H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 195.1, 161.5, 158.78 (J_{CF} = 240.0 Hz), 158.0, 151.2 (J_{CF} = 2.0 Hz), 151.0, 134.1, 129.0, 124.7, 124.4, 121.0 (J_{CF} = 8.4 Hz), 116.9 (J_{CF} = 23.4 Hz), 113.3, 97.5, 56.1, 51.6, 43.3, 30.5, 21.1. FT-IR (KBr): ν_{max} (cm^{-1}) 1685 (C═O). MS, *m*/*z* (I, %): 497, 495, 493 (M^+, 2, 3, 4); 422, 420 418 (14, 40, 42); 339, 337, 335 (21, 88, 100). HRMS (ESI) *m*/*z*: $[M + H]^+$ calcd for $C_{23}H_{23}Cl_2FN_3O_2S^+$, 498.0808, 496.0837, and 494.0867; found, 498.0802, 496.0838, and 494.0867.

*2-(6-{4-[2-(Phenylthio)ethyl]piperazin-1-yl}pyridin-3-yl)-1-pyridin-2-ylethanol (**9**, Scheme 4B).* To a solution of *N*-oxide **1z** (216 mg, 1 mmol, 1 equiv) in CH_3CN (20 mL) was added 1,4-

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diazabicyclo[2.2.2]octane (DABCO, 1.12 g, 10 mmol, 10 equiv) in one portion. To the mixture cooled to 0 °C was added a solution of trifluoroacetic anhydride (1.05 g, 700 μL, 5 mmol, 5 equiv) in CH_3CN (5 mL) dropwise. The resulting mixture was stirred for 10 h at rt. A solution of thiophehol (661 mg, 6 mmol, 6 equiv) in CH_3CN (5 mL) was slowly added, and the resulting mixture was stirred for 10 h at rt. The solvent was removed under reduced pressure, the residue was mixed with aq Na_2CO_3 (20 mL, 2 M), and the resulting mixture was stirred at rt for 3 h, CH_2Cl_2 (20 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL), all organic layers were combined and dried with Na_2SO_4, and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel using gradient mixtures of CH_2Cl_2–MeOH (20:1 to 2:1) as eluent. Yield 0.321 g (76%); yellow amorphous; R_f = 0.58 (CH_2Cl_2/CH_3OH = 5/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.53 (d, J = 4.7 Hz, 1H), 7.92 (d, J = 2.0, 1H), 7.65 (td, J = 7.7, 1.7 Hz, 1H), 7.26–7.39 (m, 6H), 7.17–7.21 (m, 2H), 6.57 (d, J = 8.6 Hz, 1H), 4.87–4.93 (m, 1H), 4.05 (br, 1H), 3.44–3.71 (m, 4H), 3.09–3.24 (m, 2H), 3.01 (dd, J = 13.9, 5.1 Hz, 1H), 2.89 (dd, J = 13.9, 7.0, 1H), 2.55–2.80 (m, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 158.3, 148.4, 148.3, 139.0, 136.6, 129.0, 128.9, 126.0, 122.5, 122.4, 120.7, 160.8, 73.8, 57.7, 52.8, 45.2, 41.0, 30.6. FT-IR (KBr): ν_{max} (cm^{-1}) 3650 (OH). MS, m/z (I, %): 420 (M^+, 3), 311 (100), 228 (77), 108 (44). Calcd for $C_{24}H_{29}N_4OS^+$, 421.2057; found, 421.2061.

*2-{[2-(4-Pyridin-2-ylpiperazin-1-yl)ethyl]thio}quinazolin-4(3H)-one (**10**, Scheme 4C).* This was synthesized using general procedure B from *N*-oxide **1b** (95 mg, 1 mmol) and sodium salt of 2-mercapto-4(3*H*)-quinazolinone prepared from 2-mercapto-4(3*H*)-quinazolinone (713 mg, 4 mmol) and NaH (60% w/w suspension, 160 mg, 4 mmol) in 5 mL of DMF with the following alterations: (a) K_2CO_3 (2.76 g, 20 mmol, 5 equiv) was added, and the reaction mixture was stirred for 30 min before addition of a nucleophile; and (b) the resulting reaction mixture was stirred at rt overnight after addition of the nucleophile. Yield 0.239 g (65%); white solid; mp: 190–193 °C; R_f = 0.47 CH_2Cl_2/CH_3OH = 10/1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.41 (br, 1H), 8.14–8.20 (m, 2H), 7.68 (t, J = 7.1 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.47 (t, J = 8.6 Hz, 1H), 7.34–7.38 (m, 1H), 6.60–6.68 (m, 2H), 3.81–3.85 (m, 4H), 3.25–3.30 (m, 2H), 2.92–2.97 (m, 2H), 2.81–2.85 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 159.4, 155.5, 149.2, 148.1, 137.7, 134.8, 126.6, 126.5, 126.1, 120.5, 113.6, 107.3, 60.4, 53.7, 44.4, 29.4. FT-IR (KBr): ν_{max} (cm^{-1}) 3220, 3196 (NH); 1695 (C=O). MS, m/z (I, %): 367 (M^+, 2), 189 (51), 121 (42), 107 (100). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{19}H_{22}N_5OS^+$, 368.1540; found, 368.1544. Characterization data obtained matched those previously reported in the literature.[9]

*Gram Scale Preparations of Thiols **11** and **12** (Scheme 4, General Procedure F).* Acetyl chloride was added portionwise to 80 mL of MeOH under stirring and cooling (−5 °C). After 1 h at rt, a solution of compound **2a** or **5a** in 20 mL of MeOH was added to the solution dropwise. The resulting mixture was stirred at rt overnight and then evaporated under reduced pressure. The residue was thoroughly washed with absolute ether and dried in vacuo.

*2-(4-Pyridin-2-ylpiperazin-1-yl)ethanethiol Dihydrochloride (**11**).* This was prepared from compound **1a** (4.17 g, 13.2 mmol) and 6.22 g (5.65 mL, 79.3 mmol, 6 equiv) of AcCl; yield 4.54 g (99%); beige solid; 197–199 °C (dec). ^{1}H NMR (400 MHz, D_2O): δ 8.43 (d, J = 9.5 Hz, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.80–7.86 (m, 2H), 7.57 (t, J = 8.1 Hz, 1H), 7.38 (d, J = 9.5 Hz, 1H), 4.14–4.34 (m, 4H), 3.58–3.72 (m, 4H), 3.48–3.52 (m, 2H), 2,94–2.96 (m, 2H). ^{13}C NMR (100 MHz, D_2O): δ 151.6, 144.5, 135.6, 133.3, 128.5, 126.2, 121.2, 117.5, 111.1, 58.7, 50.4, 43.4, 17.7. MS, m/z (I, %): 273 (M^+, 8), 240 (46), 157 (100). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{15}H_{20}N_3S^+$, 274.1372; found, 274.1374.

*2-{4-[2-(4-Pyridin-2-ylpiperazin-1-yl)ethyl]piperazin-1-yl}-ethanethiol Tetrahydrochloride (**12**).* This was prepared from compound **5a** (5.01 g, 11.7 mmol) and 7.36 g (6.69 mL, 93.7 mmol, 8 equiv) of AcCl; yield 6.04 g (97%); yellow solid; mp: 217–220 °C (dec). ^{1}H NMR (400 MHz, D_2O): δ 8.50 (J = 9.7 Hz, 1H), 7.84–7.97 (m, 3H), 7.60–7.64 (m, 1H), 7.44 (d, J = 9.7 Hz, 1H), 4.26–4.32 (m, 4H), 3.67–3.72 (m, 4H), 3.50–3.63 (m, 6H), 3.40–3.45 (m, 2H), 3.02–3.20 (m, 6H), 2.90–2.94 (m, 2H). ^{13}C NMR (100 MHz, D_2O): δ 151.9, 144.8, 135.8, 133.4, 128.6, 126.4, 121.5, 117.6, 111.3, 58.5, 51.6, 51.1, 50.2, 50.1, 49.2, 43.6, 17.6. MS, m/z (I, %): 385 (M^+, 8), 226 (82), 171 (42), 159 (100). HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{32}N_5S^+$, 386.2373; found, 386.2376.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02952.

X-ray crystallographic data for **2g** (CIF)
X-ray crystallographic data for **4a** (CIF)
Copies of ^{1}H NMR of all starting materials, copies of ^{1}H, ^{13}C NMR and MS of all new compounds, and 2D NMR spectra for **2a** (COSY (^{1}H–^{1}H), HSQC (^{1}H–^{13}C), NOESY (^{1}H–^{1}H), and HMBC (^{1}H–^{13}C)) and **2i** + **2i′** (COSY (^{1}H–^{1}H), HSQC (^{1}H–^{13}C), ROESY (^{1}H–^{1}H), and HMBC (^{1}H–^{13}C)) (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: karchava@org.chem.msu.ru.

ORCID

Dmitry I. Bugaenko: 0000-0002-5028-7244
Alexander V. Karchava: 0000-0001-9008-644X

Notes

The authors declare no competing financial interest.

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