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One-Pot Synthesis of Pyrrolo[3,2,1-*kl*]phenothiazines through Copper-Catalyzed Tandem Coupling/Double Cyclization Reaction

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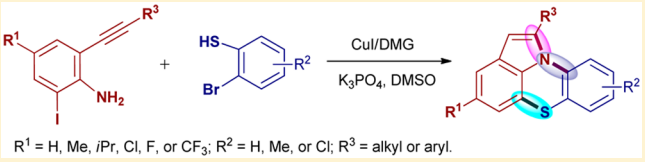
Supporting Information

ABSTRACT: A novel and efficient synthesis of pyrrolo[3,2,1-*kl*]phenothiazines has been developed through a Cu(I)-catalyzed tandem C−S coupling/double cyclization process. Using 2-alkynyl-6-iodoanilines and *o*-bromobenzenethiols as the starting materials, a wide range of pyrrolo[3,2,1-*kl*]phenothiazine derivatives were facilely and efficiently generated in one pot under Cu(I) catalysis.



Heteroaryl-fused heterocyclic scaffolds can be found in numerous useful natural products, synthetic drugs, and functional materials.[1] The existence of the polycyclic indole[2] and phenothiazine moieties[3] in many biologically active molecules and promising functional materials has stimulated the exploitation of their synthetic routes. Pyrrolo[3,2,1-*kl*]phenothiazines, which incorporate both indole and phenothiazine moieties, have aroused considerable interest in the fields of medicinal chemistry and material science. For instance, as shown in Figure 1, some pyrrolo[3,2,1-*kl*]phenothiazines (**A**)

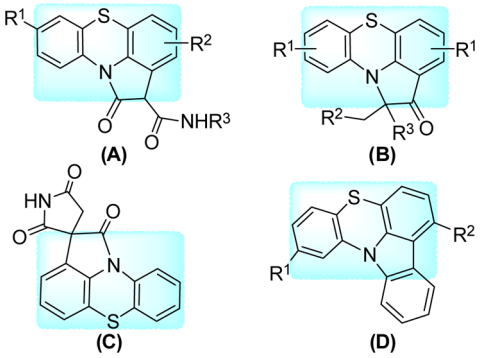


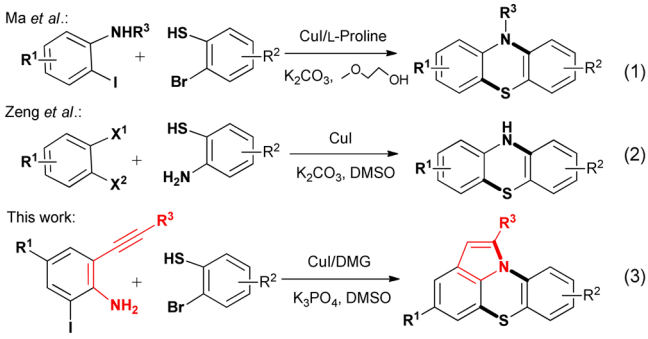
Figure 1. Several useful pyrrolophenothiazine derivatives.

display anti-inflammatory activity.[4] They also demonstrate activities as potent antiarthritis and antibronchitis agents.[5] It was claimed that heteroaromatic phenothiazines (**B**) might be a neuroleptic drug option.[6] Several pyrrolophenothiazines (**C**) can be used for the treatment of chronic diabetic disease.[7] Certain polycyclic phenothiazines (**D**) play important roles in the field of organic electroluminescent devices.[8]

Although these polycyclic heteroarenes are important, efficient synthetic approaches to substituted pyrrolo[3,2,1-*kl*]phenothiazines have rarely been documented. And previously referred routes might have some limitations such as tedious procedures, low efficiency, and/or narrow application scope.[4−9] Therefore, developing convenient and efficient approaches to a diverse range of substituted pyrrolo[3,2,1-*kl*]phenothiazines is highly desirable.

Catalytic domino transformation is a convenient and powerful method for constructing molecular complexity in a single operation.[10] And Cu-mediated domino reactions with intramolecular hydroamination[11] as the key step(s) have also been intensely investigated.[12] On the other hand, Cu-catalyzed one-pot transformations involving cross-coupling processes are efficient and facile strategies for the one-step assembly of structurally diversified molecules.[13] As shown in Scheme 1, Ma

Scheme 1. Some Related Reports on Cu-Mediated One-Pot Approaches to Phenothiazine Derivatives



et al. first discovered the Cu-catalyzed domino synthesis of phenothiazines via the C−S/C−N coupling of *o*-iodoanilines with *o*-bromothiophenols (eq 1).[14b] Then the Zeng group developed a one-pot approach to phenothiazines through Cu-catalyzed C−S/C−N coupling of aryl *o*-dihalides and *o*-aminobenzenethiols (eq 2).[14a] Although great progress has been achieved, most reports focus on the use of the substrates

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bearing one or two functional groups at an aryl ring. And there are very limited examples on the Cu-mediated one-pot assembly of polycyclic heteroarenes with the substrates bearing more than three functional groups at the same aryl ring.[15] Moreover, the use of multifunctionalized substrates in one-pot transformations would modularly produce interesting moieties that exist in numerous useful compounds. One of the greatest challenges for achieving these transformations is the compatibility of different functional groups in the same catalytic system.

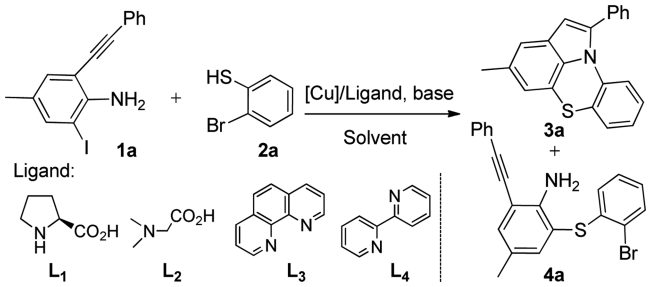
We are particularly interested in finding new one-pot transformations for the facile synthesis of various cyclic molecules under Cu catalysis.[16] Herein we report the development of a Cu-catalyzed synthesis of pyrrolo[3,2,1-*kl*]phenothiazines from 2,6-difunctionalized anilines and *o*-bromobenzenethiols through a one-pot multibond forming process. As depicted in Scheme 1, although the starting materials seem partially similar to those of the previous reports on the domino synthesis of tricyclic phenothiazines,[14] our method is quite different from theirs with regard to the following factors: (1) the products are tetracyclic pyrrolophenothiazines instead of tricyclic phenothiazines; (2) it involves a probable C−S coupling/double cyclization pathway; and (3) it presents a new strategy on applying multifunctionalized substrates to the generation of polycyclic heteroaromatics in one pot under Cu catalysis (eq 3).

We commenced our investigation with the reaction between 2-iodo-6-alkynylaniline **1a**[17] and *o*-bromobenzenethiol **2a**. Initially, treatment of substrate **1a** with **2a**, CuI (10 mol %), L-proline (20 mol %), and Cs_2CO_3 (2 equiv) in DMSO at 100 °C delivered only a 19% yield of the target product **3a**, in company with a 63% yield of the C−S coupling product **4a** (Table 1, entry 1). Increasing the temperature to 130 °C gave a moderate yield (entry 2). This tandem transformation also seemed to be sensitive to heating method. When the mixture was heated at 80 °C for 24 h and then stirred at 130 °C, **3a** was exclusively generated in 68% yield (entry 3). And a 76% yield was obtained when the mixture was stirred at 90 and 130 °C for 24 h respectively (entry 4). Switching the base to K_2CO_3 gave a deteriorated result (entry 5), whereas the use of K_3PO_4 led to a slightly better result (entry 6). A screen of different solvents identified DMSO as the best medium (entry 6 vs entries 7 and 8). A series of ligands were then studied (entries 6 and 9−12). When *N*,*N*-dimethylglycine (DMG) was used as the ligand, the yield increased to 82% (entry 9). Other ligands were inferior to DMG. A moderate yield of **3a** was produced in the absence of any ligand (entry 13). Then different Cu sources were tested, and CuI showed the best efficiency (entries 6 and 14−16). We also found that the time for stirring at 90 °C could be reduced to 18 h (entry 17), while further shortening this process caused a decline in the yield (entry 18). The structure of product **3a** was further determined by single-crystal X-ray analysis that unambiguously presented the construction of the tetracyclic pyrrolo[3,2,1-*kl*]phenothiazine moiety (see the Supporting Information, Figure S1).

With the optimized conditions in hand, we subsequently studied the substrate scope of the one-pot method (Table 2). First, a broad range of 2-iodo-6-alkynylanilines were surveyed (entries 1−12). A variety of substituted 2-iodo-6-alkynylanilines successfully afforded desired products **3**. Both aromatic (entries 1−5) and aliphatic substituents (entries 6 and 7) at the alkynyl terminal position were well tolerated under the conditions. The substrates bearing an electron-withdrawing (such as F) or a strong electron-donating group (such as MeO) at the aryl ring of the alkyne were less effective than the others (entries 3 and 4). Interestingly, the substrate with a heteroaryl ring at its alkynyl chain gave an excellent yield (entry 5). Different substituents (including Me, *i*-Pr, Cl, F, and CF_3) at the phenyl ring of the aniline were also studied (entries 1 and 8−12). The reactions of the electron-poor anilines furnished relatively lower yields than those of the electron-rich ones (entries 9−12 vs entries 1 and 8). Next, different substituted *o*-bromobenzenethiols were also studied. It was found that the reactions with *o*-bromobenzenethiols bearing either an electron-donating (Me) or electron-withdrawing group (Cl) proceeded smoothly, affording the expected products in moderate to good yields (entries 13−21).

In order to gain insight into the pathway, some control experiments were carried out (Scheme 2). After 2-iodo-6-alkylnylaniline **1a** reacted with *o*-bromobenzenethiol **2a** at 90 °C for 18 h, the C−S coupling product **4a** was exclusively isolated in 86% yield (eq 4). On further investigation we found that when the temperature was raised up to 110 °C for 8 h, a 71% yield of **4a** was obtained, accompanied by a small amount of **3a** (eq 5). In this case, neither the intermediate **5a** derived from the C−S coupling/cyclization process nor the C−S/C−N coupling product **6a** was isolated. We supposed that the intramolecular cyclization proceeded very fast under these conditions; thus, it was unfeasible to capture the intermedi-

Table 1. Optimization of the Reaction Conditions[a]



entry	[Cu]	base	L	T_1/T_2 (°C/°C)	t_1/t_2 (h/h)	yield (%)[b]
1	CuI	Cs_2CO_3	L_1	110/−	48/−	19 (63)
2	CuI	Cs_2CO_3	L_1	130/−	48/−	62 (15)
3	CuI	Cs_2CO_3	L_1	80/130	24/24	68
4	CuI	Cs_2CO_3	L_1	90/130	24/24	76
5	CuI	K_2CO_3	L_1	90/130	24/24	11 (52)
6	CuI	K_3PO_4	L_1	90/130	24/24	78
7	CuI	K_3PO_4	L_1	90/130	24/24	65[c]
8	CuI	K_3PO_4	L_1	90/130	24/36	61[d]
9	CuI	K_3PO_4	L_2	90/130	24/24	82
11	CuI	K_3PO_4	L_3	90/130	24/24	trace
12	CuI	K_3PO_4	L_4	90/130	24/24	76
13	CuI	K_3PO_4	−	90/130	24/24	52
14	CuBr	K_3PO_4	L_2	90/130	24/36	71
15	CuCl	K_3PO_4	L_2	90/130	24/24	61
16	Cu_2O	K_3PO_4	L_2	90/130	24/24	trace
17	**CuI**	**K_3PO_4**	L_2	**90/130**	**18/24**	**82**
18	CuI	K_3PO_4	L_2	90/130	12/24	78

[a]Reaction conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), Cu source (0.1 mmol), ligand (0.2 mmol), base (2.0 mmol), in DMSO (3 mL), under N_2, at T_1 °C for t_1 h and then at T_2 °C for t_2 h. [b]Isolated yield of **3a**. The isolated yield of **4a** was given in the parentheses if it was separable. [c]DMF was used as the solvent. [d]Ethylene glycol monomethyl ether was used as the solvent.

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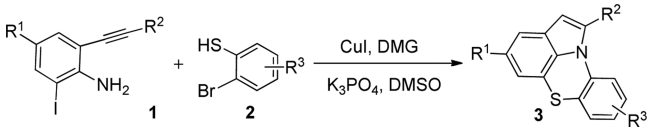
Table 2. Copper-Catalyzed One-Pot Synthesis of Pyrrolo[3,2,1-*kl*]phenothiazines[a]



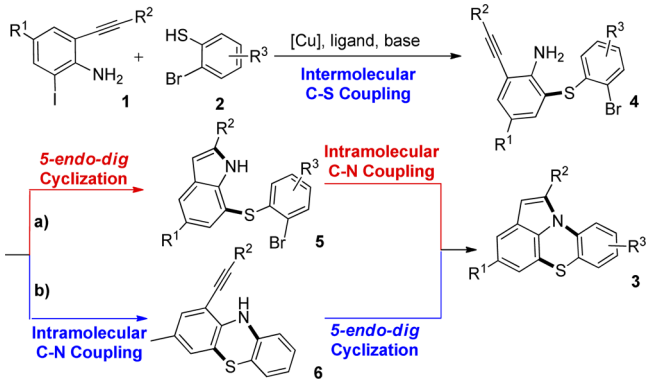
Entry	R^1	R^2	R^3	Prod. **3**	Yield (%)[b]
1	Me	Ph	H	**3a**	82
2	Me	*p*-Tol	H	**3b**	80
3	Me	*p*-FPh	H	**3c**	69
4	Me	*p*-MeOPh	H	**3d**	58
5	Me		H	**3e**	93
6	Me		H	**3f**	80
7	Me		H	**3g**	83
8	*i*-Pr	Ph	H	**3h**	76
9	Cl	Ph	H	**3i**	60
10	Cl	*p*-FPh	H	**3j**	71
11	F	Ph	H	**3k**	58
12	CF_3	Ph	H	**3l**	67
13	Me	Ph	*p*-Me	**3m**	80
14	Me	Ph	*p*-Cl	**3n**	74
15	Me	*p*-Tol	*p*-Me	**3o**	81
16	Me	*p*-FPh	*p*-Me	**3p**	72
17	Me	*p*-MeOPh	*p*-Me	**3q**	55
18	*i*-Pr	Ph	*p*-Me	**3r**	76
19	*i*-Pr	Ph	*p*-Cl	**3s**	75
20	Cl	Ph	*p*-Me	**3t**	62
21	CF_3	Ph	*p*-Me	**3u**	60

[a]Reaction conditions: 2-iodo-6-alkylnylaniline **1** (1.0 mmol), 2-bromobenzenethiol **2** (1.5 mmol), CuI (0.1 mmol), DMG (0.2 mmol), K_3PO_4 (2.0 mmol), in DMSO (3 mL), under N_2, at 90 °C for 18 h and then at 130 °C for 24 h. [b]Isolated yield of product **3**.

ate(s) of the second step. With this possibility considered, a nonhalogenated thiophenol **2d** was used. And the reaction efficiently gave 7-phenylthio indole **5b** (eq 6), indicating that C−S coupling/cyclization/C−N coupling process was a possible pathway. However, the C−S coupling/C−N coupling/cyclization process might also be involved, since the intermediate such as **6a** could not be excluded under these conditions.[14b]

Based on the above experiments and related literatures,[14b,18] a plausible pathway is depicted in Scheme 3. Under the catalysis

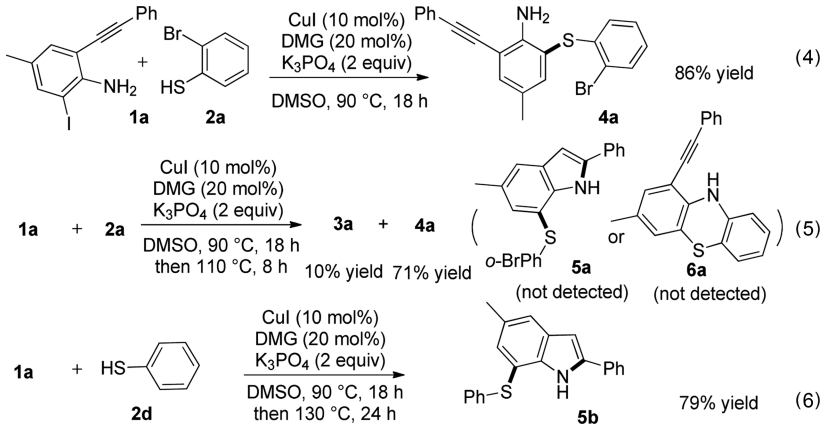
Scheme 3. Proposed Pathways for the One-Pot Synthesis of Pyrrolo[3,2,1-*kl*]phenothiazine



of Cu(I), 2-iodo-6-alkylnylaniline **1** reacted with *o*-bromobenzenethiol **2** to furnish the C−S coupling intermediate **4**. Then intermediate **4** may undergo two probable pathways: (a) a 5-*endo-dig* cyclization provided the 7-phenylthio indole-type intermediate **5**, and subsequent intramolecular C−N coupling of **5** delivered pyrrolo[3,2,1-*kl*]phenothiazine **3**; (b) the formation of 1-phenylethynyl phenothiazine-type intermediate **6** via an intramolecular C−N coupling, followed by the cyclization to afford product **3**.

In conclusion, a novel Cu(I)-catalyzed C−S coupling/double cyclization reaction has been developed for the synthesis of pyrrolo[3,2,1-*kl*]phenothiazines. Using the reactions of 2-alkynyl-6-iodoanilines and *o*-bromobenzenethiols, a wide range of the desired pyrrolo-fused phenothiazines could be efficiently synthesized. Moreover, the method provides a good example in applying the multifunctionalized substrates to the

Scheme 2. Several Control Experiments Aiming at Probing the Probable Pathway



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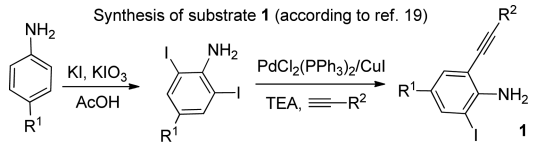
direct and modular generation of polycyclic heteroaromatics in one pot under Cu catalysis.

EXPERIMENTAL SECTION

General Information. All one-pot reactions were carried out in an oven-dried Schlenk tube equipped with a magnetic stir bar under a nitrogen atmosphere. DMF and DMSO were distilled from CaH_2; EGME was dried over Na_2SO_4 before being distilled. 2-Alkynyl-6-iodoanilines **1** were produced from the Sonogashira reactions between corresponding 2,6-diiodoanilines and terminal alkynes.[19] *o*-Bromobenzenethiols **2** were synthesized according to the known literatures.[20] All other reagents were gained from commercial sources and used without further purification, if not stated otherwise. All melting points are uncorrected. The NMR spectra were recorded in $CDCl_3$ on a 400 or 600 MHz instrument with TMS as the internal standard. Recorded shifts were reported in parts per million (δ) downfield from TMS. Data are shown as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J), and integration. TLC was carried out with 0.2 mm thick silica gel plates (GF254). Visualization was accomplished by UV light. The chromatographic columns were hand packed with silica gel 60 (200–300 mesh). Infrared spectra were recorded with an IR spectrometer and are reported in reciprocal centimeter (cm^{-1}). The unknown key products were additionally confirmed by HRMS. HRMS analyses were carried out using a TOF-MS instrument with an ESI source.

General Procedure for the Synthesis of 2-Alkynyl-6-Iodoanilines 1. An oven-dried two-necked flask was charged with a magnetic



stir bar, 4-substituted 2,6-diiodoaniline (5 mmol), $Pd(PPh_3)_2Cl_2$ (175 mg, 0.25 mmol, 5 mol %), and CuI (95 mg, 0.5 mmol, 10 mol %). The flask was evacuated and backfilled with nitrogen (three times). Under a positive pressure of nitrogen, a solution of terminal alkyne (5 mmol) in TEA (20 mL) was added via syringe. The mixture was stirred at rt for 15 h and then stirred at 50 °C for about 5 h (monitored by TLC). After being cooled to rt, the mixture was diluted with 60 mL of EtOAc. The mixture was washed with brine (10 mL × 3). Then the organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using petroleum/EtOAc (10:1, v/v) as eluent to afford substrate **1**.

General Procedure for the Copper-Catalyzed One-Pot Synthesis of Pyrrolo[3,2,1-*kl*]phenothiazines 3. An oven-dried Schlenk tube was charged with a magnetic stir bar, 2-alkynyl-6-iodoanilines **1** (0.5 mmol), CuI (0.05 mmol, 10 mol %), DMG (0.1 mmol, 20 mol %), and K_3PO_4 (2.0 mmol, 4.0 equiv). The tube was capped and then evacuated and backfilled with nitrogen (three times). Under a positive pressure of nitrogen, a solution of *o*-bromobenzenethiol **2** (0.5 mmol, 1 equiv) in DMSO (2.0 mL) was added via syringe. The mixture was stirred at 90 °C for about 18 h. Then it was stirred at 130 °C for 24 h (monitored by TLC). After being cooled to rt, the mixture was diluted with 30 mL of EtOAc. The mixture was washed with brine (10 mL × 3). Then the organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using petroleum/EtOAc (12:1–8:1, v:v) as eluent to give product **3**.

*4-Methyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3a**).* Yellow solid (128 mg, 82% yield); R_f = 0.60 (petroleum/DCM 10:1); mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2H), 7.49–7.40 (m, 3H), 7.19 (dd, J = 7.7, 1.5 Hz, 1H), 7.05 (s, 1H), 6.91 (td, J = 7.5, 1.2 Hz, 1H), 6.85–6.80 (m, 1H), 6.74 (s, 1H), 6.69 (dd, J = 8.3, 1.1 Hz, 1H), 6.59 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4, 136.4, 136.3, 133.8, 133.7, 128.8 (2 × CH), 128.3 (2 × CH), 128.1, 128.0, 127.5, 126.8, 124.1, 122.8, 119.2, 118.9, 117.5, 117.3, 109.3, 21.5; IR (KBr) ν_{max} 3054, 1589, 1460, 1326, 1217, 1141, 839, 752 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{16}NS^+$ $[M + H]^+$: 314.0998; found: 314.1010.

Important Crystal Data for 3a. $C_{21}H_{15}NS$, M = 357.47, monoclinic, space group $P\bar{1}$, a = 11.7583(8) Å, b = 12.9661(8) Å, c = 13.8658(9) Å. V = 1821.5(2) Å^3, Z = 4, T = 293(2) K, 54 551 reflections collected, 8139 independent reflections. Final R = 0.2071, wR = 0.3915, GoF = 1.267 for 8139 reflections with $I > 2\sigma(I)$ and 469 parameters. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre; deposition no. CCDC-1056785.

*4-Methyl-1-(p-tolyl)pyrrolo[3,2,1-kl]phenothiazine (**3b**).* Yellow oil (131 mg, 80% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62–7.60 (m, 2H), 7.49–7.46 (m, 2H), 7.45–7.42 (m, 1H), 7.07–7.04 (m, 2H), 6.75–6.72 (m, 2H), 6.59 (s, 1H), 6.48 (s, 1H), 2.40 (s, 3H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 136.7, 136.3, 136.0, 133.8, 133.6, 128.7 (2 × CH), 128.4 (2 × CH), 128.0, 127.7, 127.4, 124.8, 120.2, 119.1, 118.8, 117.8, 117.2, 109.0, 21.5, 21.1; IR (film) ν_{max} 3055, 2912, 1590, 1459, 1323, 1215, 1144, 841, 755 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{18}NS^+$ $[M + H]^+$: 328.1154; found: 328.1161.

*1-(4-Fluorophenyl)-4-methylpyrrolo[3,2,1-kl]phenothiazine (**3c**).* Yellow oil; (114 mg, 69% yield); R_f = 0.70 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59–7.54 (m, 2H), 7.19–7.15 (m, 3H), 7.04 (s, 1H), 6.92 (td, J = 7.6, 1.1 Hz, 1H), 6.86–6.82 (m, 1H), 6.73 (s, 1H), 6.64 (d, J = 8.3 Hz, 1H), 6.55 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.7 (d, J_{C-F} = 246.7 Hz), 139.2, 136.3, 136.2, 133.9, 130.02, 129.97 (2 × CH), 129.8, 128.2, 127.4, 126.9, 124.2, 122.9, 119.0 (d, J = 2.2 Hz), 117.5, 117.3, 115.9 (d, J_{C-F} = 21.6 Hz) (2 × CH), 109.3, 21.5; IR (film) ν_{max} 3069, 2923, 1590, 1461, 1322, 1218, 1156, 836, 749 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{15}FNS^+$ $[M + H]^+$: 332.0904; found: 332.0898.

*1-(4-Methoxyphenyl)-4-methylpyrrolo[3,2,1-kl]phenothiazine (**3d**).* Yellow oil; (100 mg, 58% yield); R_f = 0.55 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (dd, J = 8.6, 1.2 Hz, 2H), 7.17 (d, J = 7.7 Hz, 1H), 7.02 (s, 1H), 7.00 (dd, J = 8.6, 1.2 Hz, 2H), 6.90 (t, J = 7.6 Hz, 1H), 6.83 (t, J = 7.8 Hz, 1H), 6.74–6.69 (m, 2H), 6.51 (d, J = 1.2 Hz, 1H), 3.90 (d, J = 1.2 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 140.3, 136.5, 136.1, 133.7, 129.6 (2 × CH), 128.0, 127.5, 126.8, 126.2, 124.1, 122.8, 119.0, 118.6, 117.3, 117.1, 114.2 (2 × CH), 108.3, 55.4 (CH_3O), 21.5; IR (film) ν_{max} 3063, 2927, 1589, 1455, 1226, 835, 754 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{22}H_{18}ONS^+$ $[M + H]^+$: 344.1104; found: 344.1109.

*4-Methyl-1-(quinolin-2-yl)pyrrolo[3,2,1-kl]phenothiazine (**3e**).* Orange solid (170 mg, 93% yield); R_f = 0.65 (petroleum/EtOAc 5:1); mp 179–181 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.16 (s, 1H), 8.32 (d, J = 1.8 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.77–7.81 (m, 1H), 7.64–7.60 (m, 1H), 7.20 (dd, J = 7.8, 1.4 Hz, 1H), 7.08 (s, 1H), 6.91 (td, J = 7.6, 1.1 Hz, 1H), 6.81–6.75 (m, 2H), 6.74 (s, 1H), 6.65 (dd, J = 8.3, 0.9 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.0, 147.4, 136.8, 136.6, 136.0, 134.1, 134.0, 129.9, 129.5, 128.4, 128.1, 127.7, 127.42, 127.41, 127.2, 126.9, 124.5, 123.0, 119.6, 118.9, 117.7, 117.5, 110.9, 21.5; IR (KBr) ν_{max} 3057, 2915, 1617, 1576, 1446, 1304, 1254, 1155, 1019, 815, 746 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{24}H_{17}N_2S^+$ $[M + H]^+$: 365.1107; found: 365.1115.

*1-Cyclopropyl-4-methylpyrrolo[3,2,1-kl]phenothiazine (**3f**).* Yellow oil (111 mg, 80% yield); R_f = 0.50 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.3 Hz, 1H), 7.06–7.10 (m, 2H), 6.96–6.90 (m, 1H), 6.83 (s, 1H), 6.50 (s, 1H), 6.16 (s, 1H), 2.32 (s, 3H), 2.20–2.16 (m, 1H), 1.19–1.15 (m, 2H), 1.01–0.97 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 142.1, 136.6, 132.94, 132.92, 127.6, 127.0, 126.7, 124.1, 122.3, 117.0, 116.4, 116.3, 104.4, 100.0, 21.4, 12.2 (cyclopropyl-CH), 9.6 (2 × cyclopropyl-CH_2); IR (film) ν_{max} 3065, 3012, 2920, 1589, 1467, 1331, 1283, 1220, 1161, 831, 744 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{18}H_{16}NS^+$ $[M + H]^+$: 278.0998; found: 278.1013.

*1-Butyl-4-methylpyrrolo[3,2,1-kl]phenothiazine (**3g**).* Yellow oil (122 mg, 83% yield); R_f = 0.50 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42–7.39 (m, 1H), 7.11–7.06 (m, 2H), 6.93 (td, J = 7.7, 1.1 Hz, 1H), 6.86 (s, 1H), 6.51 (s, 1H), 6.27 (s, 1H),

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3.09−3.05 (m, 2H), 2.32 (s, 3H), 1.81−1.76 (m, 2H), 1.51−1.47 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.0, 136.6, 133.6, 133.0, 128.8, 127.9, 127.1, 126.9, 124.1, 122.7, 117.0, 116.5, 116.2, 105.8, 31.1, 30.9, 22.6, 21.4, 14.0; IR (film) ν_{max} 3054, 2926, 2860, 1590, 1465, 1328, 1217, 1164, 834, 741 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{19}H_{20}NS^+$ [M + H]$^+$: 294.1311; found: 294.1315.

*4-Isopropyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3h**).* Yellow oil (130 mg, 76% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64−7.58 (m, 2H), 7.49−7.45 (m, 2H), 7.44−7.40 (m, 1H), 7.20 (dd, J = 7.7, 1.4 Hz, 1H), 7.13 (s, 1H), 6.92 (td, J = 7.6, 1.1 Hz, 1H), 6.85−6.79 (m, 2H), 6.68 (d, J = 8.3 Hz, 1H), 6.63 (s, 1H), 2.98−2.94 (m, 1H), 1.33−1.32 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.4, 140.5, 136.7, 136.4, 133.8, 128.8 (2 × CH), 128.3 (2 × CH), 128.11, 128.09, 127.4, 126.8, 124.1, 122.8, 119.2, 117.5, 116.7, 114.8, 109.6, 34.4, 24.5 (2 × CH_3); IR (film) ν_{max} 3053, 2912, 1590, 1459, 1342, 1142, 751 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NS^+$ [M + H]$^+$: 342.1311; found: 342.1320.

*4-Chloro-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3i**).* Yellow solid (100 mg, 60% yield); R_f = 0.70 (petroleum/EtOAc 10:1); mp 56−58 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 6.8 Hz, 2H), 7.50−7.45 (m, 3H), 7.21−7.20 (m, 1H), 7.17−7.16 (m, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.86−6.81 (m, 2H), 6.69 (d, J = 8.3 Hz, 1H), 6.57 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.2, 136.2, 135.6, 133.1, 129.3, 128.9 (2 × CH), 128.5, 128.4 (2 × CH), 128.1, 127.7, 127.1, 124.6, 122.1, 119.6, 119.4, 117.3, 116.9, 108.8; IR (KBr) ν_{max} 3050, 1590, 1566, 1479, 1453, 1359, 1191, 1078, 748, 636 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{20}H_{13}ClNS^+$ [M + H]$^+$: 334.0452 (^{35}Cl); found: 334.0453 (^{35}Cl).

*4-Chloro-1-(4-fluorophenyl)pyrrolo[3,2,1-kl]phenothiazine (**3j**).* Yellow oil (125 mg, 71% yield); R_f = 0.60 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.6, 5.4 Hz, 2H), 7.47−7.46 (m, 1H), 7.20 (d, J = 1.6 Hz, 1H), 7.20−7.16 (m, 2H), 6.96 (t, J = 7.5 Hz, 1H), 6.88−6.83 (m, 2H), 6.65 (d, J = 8.1 Hz, 1H), 6.55 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.9 (d, J_{C-F} = 247.8 Hz) (CF), 140.1, 136.1, 135.5, 130.1 (d, J_{C-F} = 8.2 Hz) (2 × CH), 129.4, 129.3, 128.2, 127.7, 127.2, 124.7, 122.3, 119.7, 119.2, 117.4, 116.9, 116.1 (d, J_{C-F} = 21.8 Hz) (2 × CH), 108.7; IR (film) ν_{max} 3066, 1587, 1480, 1453, 1336, 1224, 1157, 1075, 837, 755, 603 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{20}H_{12}ClFNS^+$ [M + H]$^+$: 352.0358 (^{35}Cl); found: 352.0366 (^{35}Cl).

*4-Fluoro-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3k**).* Yellow oil (92 mg, 58% yield); R_f = 0.70 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60−7.59 (m, 2H), 7.49−7.43 (m, 3H), 7.17 (dd, J = 7.7, 1.4 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 6.91−6.88 (m, 1H), 6.86−6.82 (m, 1H), 6.69 (dd, J = 8.3, 1.0 Hz, 1H), 6.66 (dd, J = 9.0, 2.2 Hz, 1H), 6.60 (d, J = 1.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.5 (d, J_{C-F} = 237.9 Hz) (CF), 141.5, 135.8, 134.3, 133.3, 128.9 (2 × CH), 128.5, 128.4 (2 × CH), 128.0, 127.2 (d, J = 11.0 Hz), 127.1, 124.5, 122.0, 119.5, 119.4, 109.3 (d, J_{C-F} = 4.3 Hz), 106.0 (d, J_{C-F} = 29.4 Hz), 102.4 (d, J_{C-F} = 24.4 Hz); IR (film) ν_{max} 3049, 1589, 1478, 1461, 1347, 1166, 1072, 749 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{20}H_{13}FNS^+$ [M + H]$^+$: 318.0747; found: 318.0741.

*Phenyl-4-(trifluoromethyl)pyrrolo[3,2,1-kl]phenothiazine (**3l**).* Yellow oil (123 mg, 67% yield); R_f = 0.60 (petroleum/EtOAc 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.61 (d, J = 6.8 Hz, 2H), 7.55 (s, 1H), 7.51−7.46 (m, 3H), 7.19 (d, J = 6.9 Hz, 1H), 7.08 (s, 1H), 6.97 (t, J = 7.4 Hz, 1H), 6.86 (t, J = 7.8 Hz, 1H), 6.72 (s, 1H), 6.70 (d, J = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 139.1, 135.6, 134.2 (d, J_{C-F} = 361.6 Hz) (CF_3), 129.0 (2 × CH), 128.8, 128.7, 128.4 (2 × CH), 128.2, 127.7, 127.2, 126.3, 125.0, 122.3, 119.5, 119.4, 115.3 (d, J_{C-F} = 4.3 Hz), 113.9 (d, J_{C-F} = 3.5 Hz), 109.5; IR (film) ν_{max} 3062, 1575, 1447, 1351, 1268, 1113, 1069, 875, 753 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{21}H_{13}F_3NS^+$ [M + H]$^+$: 368.0715; found: 368.0697.

*4,9-Dimethyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3m**).* Yellow oil (131 mg, 80% yield); R_f = 0.55 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 8.1 Hz, 2H), 7.27 (d, J = 7.8 Hz, 2H), 7.17 (dd, J = 7.8, 1.5 Hz, 1H), 7.03 (s, 1H), 6.91 (td, J = 7.5, 1.2 Hz, 1H), 6.82 (td, J = 7.5, 1.2 Hz, 1H), 6.74−6.69 (m, 2H), 6.55 (s, 1H), 2.46 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 136.7, 136.3, 136.0, 133.8, 133.6, 128.7 (2 × CH), 128.4 (2 × CH), 128.1, 127.7, 127.4, 124.8, 120.1, 119.1, 118.8, 117.7, 117.1, 108.9, 21.5, 21.0; IR (film) ν_{max} 3054, 2923, 1599, 1460, 1308, 1287, 1175, 841, 761 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{22}H_{18}NS^+$ [M + H]$^+$: 328.1154; found: 328.1162.

*9-Chloro-4-methyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3n**).* Yellow oil (128 mg, 74% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59−7.57 (m, 2H), 7.51−7.48 (m, 2H), 7.47−7.44 (m, 1H), 7.07−7.04 (m, 2H), 6.88 (dd, J = 8.3, 2.1 Hz, 1H), 6.71 (s, 1H), 6.61 (d, J = 2.0 Hz, 1H), 6.59 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.3, 137.3, 136.0, 134.2, 133.0, 132.4, 129.0 (2 × CH), 128.51, 128.50, 128.3 (2 × CH), 127.6, 124.0, 121.3, 119.2, 119.1, 117.6, 117.0, 109.7, 21.5; IR (film) ν_{max} 3052, 2915, 1564, 1459, 1326, 1223, 752, 638 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{21}H_{15}ClNS^+$ [M + H]$^+$: 348.0608 (^{35}Cl); found: 348.0615 (^{35}Cl).

*4,9-Dimethyl-1-(p-tolyl)pyrrolo[3,2,1-kl]phenothiazine (**3o**).* Yellow solid (138 mg, 81% yield); R_f = 0.60 (petroleum/DCM 10:1); mp 127−130 °C. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.9 Hz, 2H), 7.05 (d, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.73 (d, J = 7.7 Hz, 1H), 6.71 (s, 1H), 6.54 (d, J = 5.6 Hz, 2H), 2.47 (s, 3H), 2.39 (s, 3H), 1.98 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 140.5, 138.0, 136.7, 136.22, 136.15, 133.6, 130.9, 129.4 (2 × CH), 128.3 (2 × CH), 127.7, 127.5, 124.8, 120.1, 119.1, 118.6, 117.7, 117.1, 108.6, 21.5, 21.4, 21.1; IR (KBr) ν_{max} 3049, 2910, 1590, 1458, 1322, 1138, 746 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NS^+$ [M + H]$^+$: 342.1311; found: 342.1318.

*1-(4-Fluorophenyl)-4,9-dimethylpyrrolo[3,2,1-kl]phenothiazine (**3p**).* Yellow oil (125 mg, 72% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59−7.55 (m, 2H), 7.17−7.15 (m, 2H), 7.06 (d, J = 7.9 Hz, 1H), 7.03 (s, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.72 (s, 1H), 6.54 (s, 1H), 6.44 (s, 1H), 2.38 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.6 (d, J_{C-F} = 248.3 Hz) (CF), 139.1, 136.8, 136.3, 135.9, 133.7, 130.06 (d, J_{C-F} = 8.1 Hz) (2 × CH), 129.9 (d, J_{C-F} = 3.4 Hz), 127.8, 127.3, 124.9, 120.0, 119.2, 118.9, 117.8, 117.1, 115.8 (d, J_{C-F} = 21.6 Hz) (2 × CH), 109.0, 21.5, 21.1; IR (film) ν_{max} 3055, 2921, 1604, 1460, 1317, 1221, 1155, 832, 802 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{22}H_{17}FNS^+$ [M + H]$^+$: 346.1060; found: 346.1066.

*1-(4-Methoxyphenyl)-4,9-dimethylpyrrolo[3,2,1-kl]phenothiazine (**3q**).* Yellow solid (98 mg, 55% yield); R_f = 0.55 (petroleum/EtOAc 10:1); mp 161−163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (d, J = 8.7 Hz, 2H), 7.05 (d, J = 7.9 Hz, 1H), 7.02−7.00 (m, 2 H), 6.99 (s, 1H), 6.73 (d, J = 7.8 Hz, 1H), 6.70 (s, 1H), 6.54 (s, 1H), 6.51 (s, 1H), 3.91 (s, 3H), 2.38 (s, 3H), 2.00 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.6, 140.2, 136.7, 136.1 (d, J = 11.9 Hz), 133.6, 133.0, 129.6 (2 × CH), 127.7, 127.5, 126.3, 124.8, 120.0, 119.1, 118.5, 117.6, 117.0, 114.1 (2 × CH), 108.1, 55.4 (CH_3O), 21.5, 21.2; IR (KBr) ν_{max} 3069, 2929, 1588, 1453, 1336, 1224, 1157, 833, 751 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{23}H_{20}NOS^+$ [M + H]$^+$: 358.1260; found: 358.1253.

*4-Isopropyl-9-methyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3r**).* Yellow oil (135 mg, 76% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62−7.59 (m, 2H), 7.49−7.46 (m, 2H), 7.44−7.42 (m, 1H), 7.12 (s, 1H), 7.07 (d, J = 7.9 Hz, 1H), 6.80 (s, 1H), 6.74 (d, J = 7.9 Hz, 1H), 6.62 (d, J = 1.8 Hz, 1H), 6.47 (s, 1H), 2.97−2.93 (m, 1H), 1.97 (s, 3H), 1.32−1.31 (m, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.2, 140.4, 136.7, 136.6, 136.0, 133.8, 128.7 (2 × CH), 128.4 (2 × CH), 128.1, 127.7, 127.3, 124.8, 120.2, 119.1, 117.8, 116.6, 114.6, 109.2, 34.4, 24.5 (2 × CH_3), 21.1; IR (film) ν_{max} 3069, 2968, 1590, 1464, 1261, 1092, 1023, 796, 750 cm^{-1}; HRMS (ESI) m/z: calcd for $C_{24}H_{22}NS^+$ [M + H]$^+$: 356.1467; found: 356.1458.

*9-Chloro-4-isopropyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3s**).* Yellow oil (141 mg, 75% yield); R_f = 0.60 (petroleum/DCM 10:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, J = 7.0 Hz, 2H), 7.51 (t, J = 7.2 Hz, 2H), 7.49−7.45 (m, 1H), 7.14 (s, 1H), 7.07 (d, J = 8.3 Hz, 1H), 6.88 (dd, J = 8.3, 2.0 Hz, 1H), 6.81 (s, 1H), 6.66−6.61 (m, 2H), 2.99−2.94 (m, 1H), 1.33 (d, J = 6.9 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 145.8, 140.5, 137.3, 136.3, 133.0, 132.4, 129.0 (2 × CH), 128.53, 128.52, 128.3 (2 × CH), 127.6, 124.0, 121.3, 119.2,

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117.1, 116.9, 115.0, 110.0, 34.4, 24.5 (2 × CH_3); IR (film) ν_{max} 3055, 2938, 1588, 1457, 1340, 1161, 748, 641 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{23}H_{19}ClNS^+$ $[M + H]^+$: 376.0921 (^{35}Cl); found: 376.0940 (^{35}Cl).

*4-Chloro-9-methyl-1-phenylpyrrolo[3,2,1-kl]phenothiazine (**3t**).* Yellow oil (107 mg, 62% yield); R_f = 0.60 (petroleum/DCM 10:1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.59 (d, *J* = 7.8 Hz, 2H), 7.50−7.45 (m, 3H), 7.20 (d, *J* = 1.4 Hz, 1H), 7.04 (d, *J* = 7.9 Hz, 1H), 6.83 (d, *J* = 1.4 Hz, 1H), 6.76 (d, *J* = 7.9 Hz, 1H), 6.57 (s, 1H), 6.47 (s, 1H), 1.96 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.2, 137.1, 136.1, 135.3, 133.2, 129.2, 128.8 (2 × CH), 128.5, 128.4 (2 × CH), 127.7, 127.6, 125.3, 120.4, 119.9, 118.5, 117.2, 116.7, 108.4, 21.1; IR (film) ν_{max} 3052, 2915, 1652, 1564, 1459, 1326, 1223, 752, 635 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{21}H_{15}ClNS^+$ $[M + H]^+$: 348.0608 (^{35}Cl); found: 348.0617 (^{35}Cl).

*9-Methyl-1-phenyl-4-(trifluoromethyl)pyrrolo[3,2,1-kl]phenothiazine (**3u**).* Yellow oil (114 mg, 60% yield); R_f = 0.60 (petroleum/EtOAc 10:1); ^1H NMR (600 MHz, $CDCl_3$) δ 7.60 (dd, *J* = 7.8, 1.5 Hz, 2H), 7.54 (s, 1H), 7.51−7.47 (m, 3H), 7.08−7.03 (m, 2H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.70 (s, 1H), 6.49 (s, 1H), 1.97 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.6, 139.0, 137.2, 134.0 (d, J_{C-F} = 299.6 Hz) (CF_3), 128.9 (2 × CH), 128.8, 128.5 (2 × CH), 128.4, 127.8, 126.34, 126.28, 125.6, 121.3, 120.5, 119.7, 118.6, 115.1 (d, *J* = 4.4 Hz), 113.7 (d, *J* = 3.6 Hz), 109.2, 21.1; IR (film) ν_{max} 3053, 2920, 1601, 1468, 1338, 1268, 1152, 1117, 804, 765, 694 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{22}H_{15}F_3NS^+$ $[M + H]^+$: 382.0872; found: 382.0857.

*2-((2-Bromophenyl)thio)-4-methyl-6-(phenylethynyl)aniline (**4a**).* Yellow vicious oil (170 mg, 86% yield); ^1H NMR (600 MHz, $CDCl_3$) δ 7.58−7.52 (m, 3H), 7.41−7.36 (m, 4H), 7.33 (s, 1H), 7.19−7.13 (m, 1H), 7.05−7.00 (m, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 148.1, 138.8, 137.6, 135.0, 132.9, 131.51 (2 × CH), 131.50, 128.5 (2 × CH), 127.9, 127.3, 126.42, 126.39, 123.0, 120.8, 112.8, 108.6, 95.2 (C, alkynyl), 85.7 (C, alkynyl), 20.1; IR (film) ν_{max} 3478, 3376, 3069, 2917, 2197, 1574, 1446, 1232, 750, 691, 579 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{21}H_{17}BrNS^+$ $[M + H]^+$: 396.0239 (^{81}Br); found: 396.0246 (^{81}Br).

*5-Methyl-2-phenyl-7-(phenylthio)-1H-indole (**5b**).* Yellow vicious oil (124 mg, 79% yield); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.52 (s, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.38−7.31 (m, 2H), 7.30−7.25 (m, 2H), 7.24−7.15 (m, 3H), 6.84 (d, *J* = 2.0 Hz, 1H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.96, 136.95, 132.0, 130.8, 130.5, 130.0, 129.2 (2 × CH), 129.0 (2 × CH), 127.9, 127.2 (2 × CH), 125.8, 125.2 (2 × CH), 122.0, 112.7, 100.1, 21.4; IR (film) ν_{max} 3471, 3058, 2959, 1603, 1582, 1452, 1238, 1076, 1024, 737, 689 cm^{-1}; HRMS (ESI) *m/z*: calcd for $C_{21}H_{18}NS^+$ $[M + H]^+$: 316.1154; found: 316.1165.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01745.

Copies of ^1H NMR and ^{13}C NMR spectra for the products and key intermediates, and X-ray crystal structure of product **3a** (PDF)

Crystallographic data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For selected reviews on some useful heteroaromatic-fused heterocyles, see: (a) Dsouza, R. N.; Pischel, U.; Nau, W. M. *Chem. Rev.* **2011**, *111*, 7941. (b) Henriques, B. J.; Rikke, K. O.; Bross, P.; Gomes, C. M. *Curr. Med. Chem.* **2010**, *17*, 3842.

(2) Selected reports on the polycyclic indoles with biological activities: (a) Brancale, A.; Silvestri, R. *Med. Res. Rev.* **2007**, *27*, 209. (b) Tanaka, M.; Sagawa, S.; Hoshi, J.-I.; Shimoma, F.; Yasue, K.; Ubukata, M.; Ikemoto, T.; Hase, Y.; Takahashi, M.; Sasase, T.; Ueda, N.; Matsushita, M.; Inaba, T. *Bioorg. Med. Chem.* **2006**, *14*, 5781. Selected reports on the polycyclic indoles that are useful in the field of functional materials: (c) Yan, L.; Zhao, D.; Lan, J.; Cheng, Y.; Guo, Q.; Li, X.; Wu, N.; You, J. *Org. Biomol. Chem.* **2013**, *11*, 7966. (d) Baik, C.; Kim, D.; Kang, M.-S.; Song, K.; Kang, S. O.; Ko, J. *Tetrahedron* **2009**, *65*, 5302.

(3) For selected references on the applications of phenothiazines in medicinal chemistry and photoelectric science, see: (a) Matralis, A. N.; Kourounakis, A. P. *J. Med. Chem.* **2014**, *57*, 2568. (b) Yang, C.-J.; Chang, Y. J.; Watanabe, M.; Hon, Y.-S.; Chow, T. J. *J. Mater. Chem.* **2012**, *22*, 4040. (c) Korth, C.; May, B. C. H.; Cohen, F. E.; Prusiner, S. B. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 9836. (d) Khan, M. O. F.; Austin, S. E.; Chan, C.; Yin, H.; Marks, D.; Vaghjiani, S. N.; Kendrick, H.; Yardley, V.; Croft, S. L.; Douglas, K. T. *J. Med. Chem.* **2000**, *43*, 3148.

(4) (a) Isakson, P. C.; Anderson, G. D.; Gregory, S. A. US patent 6136839; *Chem. Abstr.* 2000, *133*, 321880. (b) Isakson, P. C.; Anderson, G. D.; Gregory, S. A. World patent 9641626; *Chem. Abstr.* 1997, *126*, 166479. (c) Mylari, B. L.; Carty, T. J.; Moore, P. F.; Zembrowski, W. J. *J. Med. Chem.* **1990**, *33*, 2019.

(5) Mylari, B. L.; McManus, J. M.; Lombardino, J. G. European patent 0332364, *Chem. Abstr.*: 1990, *112*, 118796.

(6) Earl, R. A.; Myers, M. J. World patent 9409009. *Chem. Abstr.* **1994**, *121*, 108835.

(7) Irikura, T.; Takagi, K.; Fujimori, S.; Hirata, Y. US patent 4593092; *Chem. Abstr.* 1986, *105*, 114900.

(8) Hikime, M.; Miura, N.; Ono, K.; Sekine, N.; Hakoi, Y. Japanese patent 2012248663, *Chem. Abstr.*: 2012, *158*, 91908.

(9) Steps from special polycyclic substrates such as phenothiazines: (a) Silva, G. A.; Costa, L. M. M.; Brito, F. C. F.; Miranda, A. L. P.; Barreiro, E. J.; Fraga, C. A. M. *Bioorg. Med. Chem.* **2004**, *12*, 3149. (b) Hollins, R. A.; Pinto, A. C. *J. Heterocycl. Chem.* **1978**, *15*, 711. (c) Boekelheide, V.; Hollins, R. A. *J. Org. Chem.* **1971**, *36*, 2437 Generally, only relevant unsubstituted or monosubstituted pyrrolo-phenothiazines were synthesized under strong acidic/basic conditions..

(10) For selected reports on domino reactions, see: (a) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2006. For some representative reports on catalytic domino synthesis of related heterocycles: (c) Synthesis of indoles via various Pd-catalyzed domino reactions: Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (d) Synthesis of indoles *via* Pd-catalyzed annulation of *o*-haloanilines with internal alkynes: Larock, R.; Yum, E.; Refvik, M. *J. Org. Chem.* **1998**, *63*, 7652. (e) Synthesis of phenothiazines through Pd-catalyzed multicomponent reactions of aryl *o*-dihalides, primary amines, and *o*-bromobenzenethiols: Dahl, T.; Tornøe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jorgensen, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 1726. (f) Synthesis of phenothiazines *via* Fe-catalyzed reactions between aryl *o*-dihalides and *N*-acyl *o*-aminobenzenethiols: Hu, W.; Zhang, S. *J. Org. Chem.* **2015**, *80*, 6128.

(11) Two important reviews on the application of intramolecular hydroaminations: (a) Muller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.

(12) Some selected recent examples on copper-catalyzed domino reaction with intramolecular hydroamination as the key step(s): (a) Cacchi, S.; Fabrizi, G.; Iazzetti, A.; Molinaro, C.; Verdiglione, R.; Goggiamani, A. *Adv. Synth. Catal.* **2015**, *357*, 1053. (b) Kumar, A.; Kumar, M.; Maurya, S.; Khanna, R. S. *J. Org. Chem.* **2014**, *79*, 6905.

DOI: 10.1021/acs.joc.5b01745
J. Org. Chem. 2015, 80, 11108−11114

(c) Xing, Y.; Cheng, B.; Wang, J.; Lu, P.; Wang, Y. *Org. Lett.* **2014**, *16*, 4814. (d) Naresh, G.; Kant, R.; Narender, T. *Org. Lett.* **2014**, *16*, 4528.
(13) For important reviews, see: (a) Liu, Y.; Wan, J. *Chem. - Asian J.* **2012**, *7*, 1488. (b) Liu, Y.; Wan, J. *Org. Biomol. Chem.* **2011**, *9*, 6873.
(14) (a) Dai, C.; Sun, X.; Tu, X.; Wu, L.; Zhan, D.; Zeng, Q. *Chem. Commun.* **2012**, *48*, 5367. (b) Ma, D.; Geng, Q.; Zhang, H.; Jiang, Y. *Angew. Chem., Int. Ed.* **2010**, *49*, 1291.
(15) The reports on the Cu-mediated one-pot synthesis of heterocycles with the substrates bearing three or more functional groups at an aryl ring: (a) Okano, K.; Mitsuhashi, N.; Tokuyama, H. *Chem. Commun.* **2010**, *46*, 2641. (b) Suzuki, Y.; Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *J. Org. Chem.* **2009**, *74*, 4246. (c) Lu, B.; Wang, B.; Zhang, Y.; Ma, D. *J. Org. Chem.* **2007**, *72*, 5337. (d) Jia, W.; Wang, R.; Song, D.; Ball, S. J.; McLean, A. B.; Wang, S. *Chem. - Eur. J.* **2005**, *11*, 832. Note that in most cases (excepting ref 13a), only symmetric multifunctionalized substrates were utilized. Reference 13a reported an interesting Cu-catalyzed double amination of the unsymmetric multifunctionalized substrates in the total synthesis of PDE-II.
(16) (a) Gao, J.; Shao, Y.; Zhu, J. Y.; Zhu, J. Q.; Mao, H.; Wang, X.; Lv, X. *J. Org. Chem.* **2014**, *79*, 9000. (b) Yuan, G.; Liu, H. Q.; Gao, J.; Xu, H.; Jiang, L.; Wang, X.; Lv, X. *RSC Adv.* **2014**, *4*, 21904. (c) Yuan, G.; Liu, H.; Gao, J.; Yang, K.; Niu, Q.; Mao, H.; Wang, X.; Lv, X. *J. Org. Chem.* **2014**, *79*, 1749. (d) Niu, Q.; Mao, H.; Yuan, G.; Gao, J.; Liu, H.; Tu, Y.; Wang, X.; Lv, X. *Adv. Synth. Catal.* **2013**, *355*, 1185.
(17) The substrates **1** can be readily and efficiently synthesized from the Sonogashira reactions of the corresponding diiodoanilines with terminal alkynes. For details, see the Experimental Section.
(18) It was reported that unmodified *o*-alkynylanilines could smoothly undergo cyclization to afford the 1*H*-indoles facilitated by copper/base in strong polar solvents: (a) Koradin, C.; Dohle, W.; Rodriguez, A. L.; Schmid, B.; Knochel, P. *Tetrahedron* **2003**, *59*, 1571. (b) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 2488−2490.
(19) Capelli, L.; Manini, P.; Pezzella, A.; d'Ischia, M. *Org. Biomol. Chem.* **2010**, *8*, 4243.
(20) Xiao, W.; Alper, H. *J. Org. Chem.* **1999**, *64*, 9646.

DOI: 10.1021/acs.joc.5b01745
J. Org. Chem. 2015, 80, 11108−11114