JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.0c00562 • Publication Date (Web): 23 Mar 2020

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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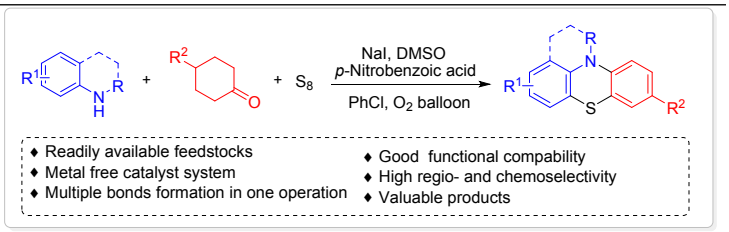
ABSTRACT: Herein, a new iodide-mediated three-component annulation reaction of secondary anilines, cyclohexanones and elemental sulfur is demonstrated, which allows access to various phenothiazines with the merits of formation of multiple chemical bonds in one single operation, high step and atom efficiency, readily available feedstocks and catalyst system, good substrate and functional group compability. The developed chemistry capable of constructing novel phenothiazines with structural diversity offers a significant basis for further applications.



■ INTRODUCTION

Phenothiazines constitute a class of highly important heterocyclic compounds. With the observation of diverse biological and therapeutic activities, such compounds have been extensively employed for the development of biomedical products, such as antitubercular and multiple drug resistance (MDR) reverting agents (Figure 1, compound **A**), cholinesterase inhibitors, and antihistaminics.[1] To date, more than 100 phenothiazine derivatives (e.g., marketing drug **B:** Chlorpromazine) have been utilized for the treatment of psychotic diseases.[2] Due to the high electron-donating capability and the nonplanar butterfly conformation inhibiting molecular aggregation, phenothiazines are promising materials utilized as light-emitting diodes, photovoltaic cells and photosensitisers.[3] Recently, such compounds have been successfully developed as cathode materials of flow batteries (compound **C**) and polymerization inhibitors and mediators in hair dye (compound **D**)[4].

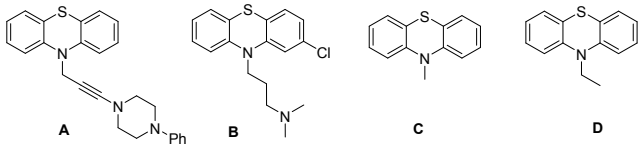
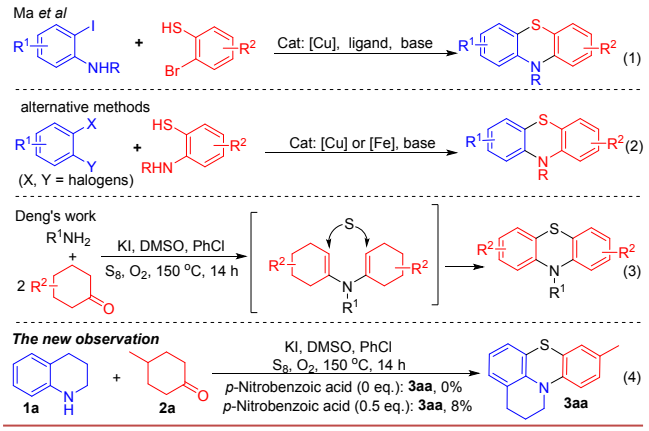


Figure 1. Representative examples

Due to the extensive functions, considerable attention has been directed toward the construction of phenothiazines over the past decades. In 2008, an early example via palladium-catalyzed three-component coupling of bromothiophenols, primary amines and 1-bromo-2-iodobenzene was reported by the Jørgensen group.[5] After that, several approaches have also been elegantly developed. For instance, Ma *et al* reported a protocol via copper-catalyzed cascade C–S and C–N bond formations of *ortho*-halogenated anilines with *ortho*-halogenated thiols (Scheme 1, eq 1).[6] Alternatively, the cross-coupling of 1,2-dihalogenated (hetero)arenes and *ortho*-aminobenzenethiols (or its surrogates) offers useful ways to achieve the related end (eq 2).[7] Despite the significant utility, these transformations generally suffer from one or more limitations such as the need for pre-installation steps to access requisite coupling reactants, the use of transition metal catalysts and less environmentally benign halogenated substrates, and low step and atom-efficiency. To overcome these issues, the Deng group has developed a four-component approach via a key iodide-mediated sulfuration of two *β*-sites of enamines, arising from the condensation of amines and two molecules of cyclohexanones (eq 3).[8] However, such a method is more applicable for access to symmetrical phenothiazines. In this context, the development of new and transition metal-free shortcuts, enabling access to both symmetrical and unsymmetrical phenothiazines, especially for those of structural novel ones, would be highly desirable, as it would offer the potential for the discovery of functional products with original physical and chemical properties.

Scheme 1. The Previous Work and Our New Observation



■ RESULTS AND DISCUSSION

To form an efficient reaction system, we chose the synthesis of phenothiazine **3aa** from THQ **1a**, 4-methylcyclohexanone **2a** and S_8 as a model system to evaluate different reaction parameters. At first, the reaction charged with a O_2 balloon, 4.0 equivalents of DMSO and 0.5 equivalent of *p*-nitrobenzoic acid was performed in chlorobenzene at 150 °C for 16 h, and several iodide catalysts were tested (Table 1, entries 1-3). The results showed that the use of NaI was the best choice. Then, we examined several acidic additives, but they were inferior to *p*-

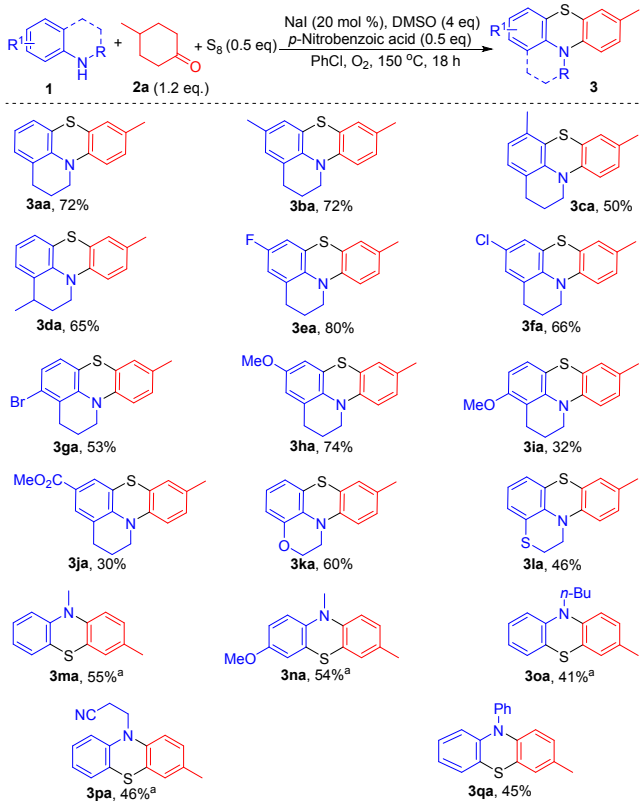
nitrobenzoic acid, and the use of base failed to afford any product (entries 4-8). The absence of DMSO had a detrimental influence on the yield (entry 9). Further, replacing S_8 with K_2S or $Na_2S_2O_3$ (entry 10), or the use of other polar solvents (entry 11) was unable to yield product **3aa**, and increase of S_8 loading could not improve the yield (entry 12). Gratifyingly, prolonging the reaction time to 18 h resulted in an optimal yield (entry 13).

Table 1. Optimization of the Reaction Conditions[a]

Entry	Cat.	Additive	S source	Yield% of **3aa**[b]
1	I_2	*p*-Nitrobenzoic acid	S_8	13
2	NIS	*p*-Nitrobenzoic acid	S_8	28
3	NaI	*p*-Nitrobenzoic acid	S_8	71
4	NaI	Benzoic acid	S_8	61
5	NaI	*p*-TSA	S_8	22
6	NaI	*L*-proline	S_8	<5
7	-	HI	S_8	12
8	NaI	K_2CO_3	S_8	0
9	NaI	*p*-Nitrobenzoic acid	S_8	53[c]
10	NaI	*p*-Nitrobenzoic acid	K_2S or $Na_2S_2O_3$	0
11	NaI	*p*-Nitrobenzoic acid	S_8	0[d]
12	NaI	*p*-Nitrobenzoic acid	S_8	68[e]
13	**NaI**	***p*-Nitrobenzoic acid**	**S_8**	**82**[f]

[a]Reaction conditions: unless otherwise stated, all the reactions charged with an O_2 balloon were performed with **1a** (0.25 mmol), **2a** (0.30 mmol), S_8 (0.5 eq), catalyst (20 mol %), additive (0.5 eq), DMSO (4.0 eq), solvent (2.0 mL) at 150 °C for 16 h. [b]GC yield using n-hexadecane as an internal standard. [c]Without DMSO. [d]Use of DMF, DMSO, NMP as the solvents. [e]S_8 (2 eq). [f]18 h.

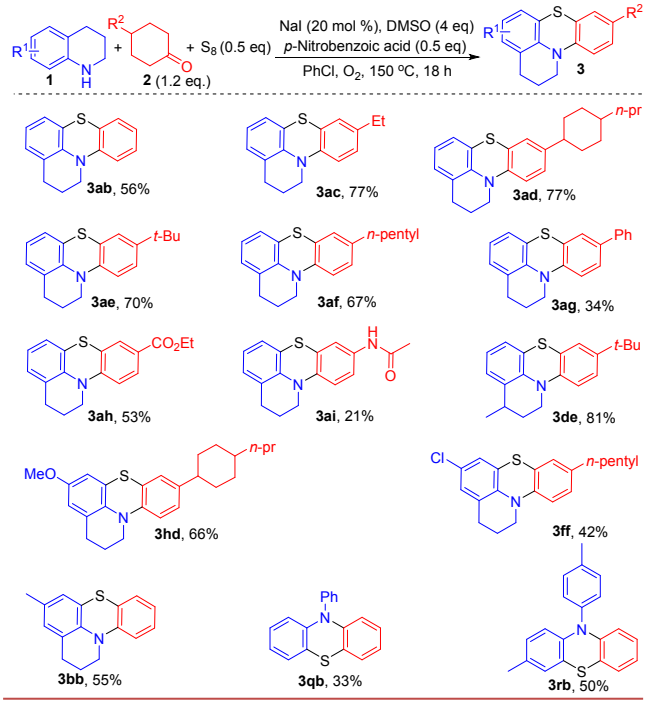
Scheme 2. Variation of THQs



[a]Using I_2 (20 mol %) instead of NaI

With the optimal (standard) conditions in hand (Table 1, entry 13), we then examined the generality of the developed synthetic protocol. First, various tetrahydroquinolines (**1**) in combination with 4-methylcyclohexanone **2a** were tested. As shown in Scheme 2, all the reactions proceeded smoothly and furnished the desired 2,3-dihydro-1*H*-pyrido[3,2,1-*kl*]phenothiazines in moderate to good yields upon isolation (**3aa-3ja**). Various functional groups on the benzene ring of THQs **1** (–Me, –OMe, –F, –Cl, –Br, $–CO_2Me$) were well tolerated in the transformation, which would offer the potential for molecular complexity via further chemical transformations. Moreover, these functionalities affected the reaction to some extent. In general, THQs having an electron-donating or weak electron-withdrawing group (**3ba-3ha**) afforded desirable yields, whereas THQs containing an strong electron-withdrawing substituent gave no product (e.g. $–NO_2$ and $–CF_3$) or low ($–CO_2Me$, **3ja**: 30%) product yield. This phenonmenon reveals that the presence of a relatively electron-rich THQ is essential for the present annulation reaction. Upon GC-MS analysis, the low yield of 5-MeO-substitutited THQ is assigned to partial decomposition of such a THQ during the reaction (**3ia**). In addition to THQs, other secondary anilines, inculding benzocyclic amines (**3ka-3la**), N-alkylanilines (**3ma-3pa**) and diarylamines (**3qa**) were also amenable to the transformation, affording the desired products in moderate yields.

Scheme 3. Variation of THQs and Secondary Anilines

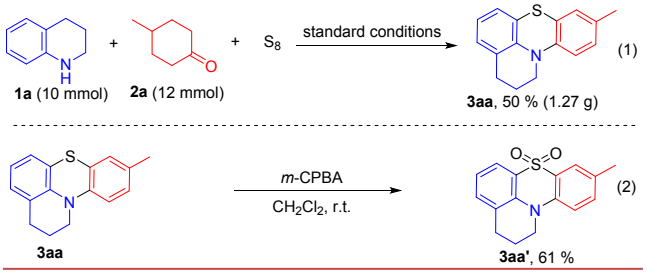


Subsequently, we turned our attention to the variation of both THQs and cyclohexanones (**2b-2i**, see Scheme S1 in SI for structures). Gratifyingly, all the substrates underwent efficient three-component annulation reaction and afforded the desired products in moderate to high yields (Scheme 3). Different substituents on cyclohexanones **2** were well tolerated (alkyl, –Ph, $–CO_2Et$, –NHCOMe), and the phenyl and amino groups led to relatively low product yields due to the occurrence of partial dehydroaromatization of such cyclohexanones. Noteworthy, 4'-propyl-[1,1'-bi(cyclohexan)]-4-one **2d**, a key component frequently employed for the preparation of liquid crystal materials,[12] also smoothly reacted with elemental sulphur and

THQs (**1a** and **1h**), affording the desired products (**3ad** and **3hd**) in good yields. In addition, it is important to note that 10-phenyl-10*H*-phenothiazine (**3qb**), a photocatalyst extensively employed for radical polymerization[13] and radical dehalogenations[14], could be prepared in one single operation with our developed approach. Such a transition metal-free streamline synthesis is far superior to the conventional approach via ruthenium-catalyzed cross-coupling of phenothiazine and anhydrous chlorobenzene with excess *t*-BuONa.[13]

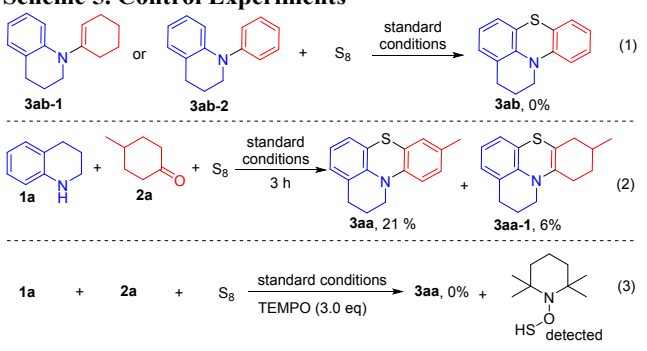
To show the practicality of the developed synthetic protocol, a gram-scale synthesis of ring-fused phenothiazine **3aa** was achieved under the standard conditions by scaling up reactants **1a** and **2a** to 10 mmol and 12 mmol, respectively (Scheme 4, eq 1). Moreover, in consideration that the introduction of sulfonyl group into organic molecules would significantly change their electron distribution and result in some interesting properties including new bioacitvities,[15] we herein could efficiently convert compound **3aa** to its sulfonyl counterpart in CH_2Cl_2 by using *m*-chloroperbenzoic acid (*m*-CPBA) as an oxidant at room temperature (eq 2).

Scheme 4. Gram-Scale Synthesis



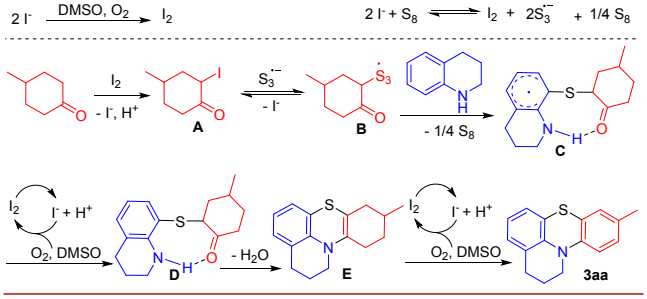
In an effort to gain mechanistic insights into the reaction, we conducted several control experiments. Subjection of 1-(cyclohex-1-en-1-yl)-1,2,3,4-tetrahydroquinoline **3ab-1** or 1-phenyl-1,2,3,4-tetrahydroquinoline **3ab-2** with sulfur or with additional aniline **1a** and cyclohexanone **2b** under the standard conditions failed to yield the annulation product **3ab** (Scheme 5, eq 1), indicating that compounds **3ab-1** and **3ab-2** serving as the reaction intermediates can be rule out. Interruption of the model reaction after 3 h generated **3aa** and a cyclization compound **3aa-1** in 21% and 6% yields, respectively (eq 2), and compound **3aa-1** was consumed up after prolonging the reaction time to 18 h, indicating that compound **3aa-1** is a key reaction intermediate. Further, the addition of excess TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy) to the model reaction completely suppressed the product formation, and TEMPO trapping a thiol group was observed by GC-MS analysis (eq 3), which suggests that the reaction involves sulfur radicals.

Scheme 5. Control Experiments



Although the mechanistic details are not fully elucidated at the current stage, a plausible reaction pathway is depicted in Scheme 6 on the basis of the above findings. At first, the oxidation of NaI with DMSO and O_2 generates molecular I_2. Moreover, the single electron transfer from I^- to S_8 would generate I_2 and trisulphur radical ion $S_3^{\cdot-}$.[16] The I_2-mediated α-iodination[17] of 4-methylcyclohexanone **2a** (see **A**) followed by nucleophilic substitution by $S_3^{\cdot-}$ forms sulfur radical **B**.[18] Then, the radical addition of **B** to the C8-site of THQ **1a** under the assistance of H-bonding and I_2-induced single electron oxidation of the coupling adduct **C** gives intermediate **D**. Finally, the intramolecular dehydrative cyclization followed by I_2-mediated dehydroaromatization of **E** gives rise to the desired product **3aa**.

Scheme 6. Plausible Reaction Pathway



■ CONCLUSIONS

In summary, we have developed a new iodide-mediated three-component annulation reaction. Various secondary anilines, including tetrahydroquinolines, benzocyclic amines, N-alkylanilines and diarylamines, were efficiently transformed in combination with cyclohexanones and elemental sulfur into the phenothiazine derivatives. The synthetic protocol features formation of multiple chemical bonds in one single operation, high step and atom efficiency, readily available feedstocks and catalyst system, good substrate and functional group compability, which offers a practical platform for access to various phenothiazines. Due to the significant importance of phenothiazines in medicinal and biological chemistry, functional materials, and photocatalysis, the developed method capable of constructing novel phenothiazines with structural diversity offers a significant basis for further discovery of new applications.

■ EXPERIMENTAL SECTION

General information. All the obtained products were characterized by melting points (m.p.), ^{1}H-NMR, ^{13}C-NMR and infrared spectra (IR). MS analyses were performed on an Agilent 5975 GC-MS instrument (EI). High-resolution mass spectra (HRMS) were recorded using electrospray ionization (ESI) and time-of-flight (TOF) mass analysis. Melting points were measured on an Electrothemal SGW-X4 microscopy digital melting point apparatus and are uncorrected; IR spectra were recorded on a FTLA2000 spectrometer; ^{1}H-NMR and ^{13}C-NMR spectra were obtained on Bruker-400/500 and referenced to 7.26 ppm for chloroform solvent with TMS as internal standard (0 ppm) or 2.50 ppm for DMSO-*d6*. Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m); TLC was performed using commercially prepared 100-400 mesh silica

gel plates (GF254), and visualization was effected at 254 nm; Unless otherwise stated, all the reagents were purchased from commercial sources, used without further purification.

Substrates preparation. All the utilized 1,2,3,4-tetrahydroquinolines are known compounds, which were purchased from commercial sources or prepared via the literature procedures.[19] Cyclohexanones, N-alkylanilines, and diarylamines were all purchased form Energy Chemic, J&K Chemic, TCI, Fluka, Acros, Bidepharm, SCRC.

Typical procedure for the synthesis of 3aa. The mixture of 1,2,3,4-tetrahydroquinoline **1a** (33.2 mg, 0.25 mmol), 4-methylcyclohexanone **2a** (33.6 mg, 0.30 mmol), S_8 (32.0 mg, 0.125 mmol), NaI (7.5 mg, 0.05 mmol), *p*-Nitrobenzoic acid (20.9 mg, 0.125 mmol), and DMSO (78.0 mg, 1.00 mmol) in PhCl (2.0 mL) was stirred in a 50 mL Schleck tube at 150 °C in an oil bath for 18 h under O_2 atmosphere (using an O_2 balloon). After cooling down to room temperature, the resulting mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica gel eluting with petroleum ether, **3aa** was afforded as a light yellow liquid (45.5 mg, 72% yield).

Gram-scale synthesis of 3aa. The mixture of 1,2,3,4-tetrahydroquinoline **1a** (1.33 g, 10 mmol), 4-methylcyclohexanone **2a** (1.35 g, 12 mmol), S_8 (1.28 g, 5 mmol), NaI (0.30 g, 2 mmol), *p*-Nitrobenzoic acid (0.84 g, 5 mmol), and DMSO (3.1 g, 40 mmol) in PhCl (80 mL) was stirred in a 350 mL Schleck tube at 150 °C in an oil bath for 18 h under O_2 atmosphere (using an O_2 balloon). After cooling down to room temperature, the resulting mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica gel eluting with petroleum ether, **3aa** was afforded as a light yellow liquid (1.27 g, 50% yield).

Analytic data of the obtained compounds. *9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3aa**)*: Light yellow liquid, PE as the eluent, 45.5 mg, 72% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.90 (d, *J* = 5.7 Hz, 3H), 6.82 (d, *J* = 7.4 Hz, 1H), 6.74 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 3.65 – 3.54 (m, 2H), 2.72 (t, *J* = 6.0 Hz, 2H), 2.22 (s, 3H), 2.11 (p, *J* = 5.8 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 142.3, 141.5, 131.8, 127.8, 127.8, 127.6, 125.3, 124.9, 121.7, 121.5, 120.0, 112.6, 47.0, 28.2, 21.8, 20.3; IR (KBr): 3018, 2928, 2956, 1496, 1443, 1315, 1256, 1187, 800, 764, 730, 604, 553 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NS$ 254.0998; Found 254.0996.

*5,9-dimethyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ba**)*: Light yellow liquid, PE as the eluent, 47.9 mg, 72% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (s, 2H), 6.78 (s, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.69 (s, 1H), 3.67 – 3.62 (m, 2H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.27 (s, 3H), 2.22 (s, 3H), 2.15 (p, *J* = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.5, 139.0, 131.4, 131.0, 128.4, 127.8, 127.5, 125.7, 124.7, 121.5, 119.9, 112.4, 46.9, 28.2, 21. 9, 20.3, 20.2; IR (KBr): 3015, 2923, 2852, 1497, 1460, 1319, 1257, 1189, 854, 800, 731, 564 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NS$ 267.1082; Found 267.1073.

*6,9-dimethyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ca**)*: Light yellow liquid, PE as the eluent, 33.5 mg, 50% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.96 (d, *J* = 8.3, 1H), 6.81 – 6.70 (m, 3H), 3.71 – 3.66 (m, 2H), 2.76 (t, *J* = 5.5 Hz, 2H), 2.34 (s, 3H), 2.16 – 2.10 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.7, 141.4, 133.3, 131.6, 127.9, 127.8, 127.1, 123.0, 122.6, 121.8, 120.5, 112.5, 47.1, 28.1, 21.7, 20.3, 20.0; IR (KBr): 3016, 2927, 2851, 1640, 1495, 1447, 1352, 1321, 1259, 1208, 1119, 925, 870, 797, 564, 512 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NS$ 267.1082; Found 267.1071.

*3,9-dimethyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3da**)*: Brownish liquid, PE as the eluent, 43.5 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.98 (d, *J* = 7.3 Hz, 2H), 6.95 (s, 2H), 6.87 – 6.76 (m, 2H), 3.75 – 3.64 (m, 2H), 2.94 (h, *J* = 6.8 Hz, 1H), 2.27 (s, 3H), 2.24 – 2.17 (m, 1H), 1.96 – 1.88 (m, 1H), 1.34 (d, *J* = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.3, 141.1, 131.9, 129.7, 127.8, 127.5, 126.6, 125.3, 121.9, 121.6, 119.8, 112.7, 43.5, 31.0, 29.0, 21.4, 20.3; IR (KBr): 2955, 2921, 2860, 1496, 1469, 1434, 1313, 1247, 1190, 801, 773, 735, 553 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NS$ 267.1082; Found 267.1072.

*5-fluoro-9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ea**)*: Light yellow liquid, PE as the eluent, 53.9 mg, 80% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, *J* = 8.3 Hz, 1H), 6.94 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.60 (d, *J* = 8.3 Hz, 1H), 3.66 (t, *J* = 5.2 Hz, 2H), 2.75 (t, *J* = 5.9 Hz, 2H), 2.27 (s, 3H), 2.17 – 2.11 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 157.9 (d, *J* = 242.4 Hz), 142.4, 137.8 (d, *J* = 3.0 Hz), 131.9, 128.1, 127.6, 126.0 (d, *J* = 8.1 Hz) , 122.1 (d, *J* = 8.1 Hz), 121.0, 113.86 (d, *J* = 22.2 Hz), 112.6, 111.9 (d, *J* = 24.2 Hz), 46.7, 28.3, 21.5, 20.2; ^{19}F NMR (376 MHz, $CDCl_3$): δ –123.9; IR (KBr): 2940, 2852, 1451, 1314, 1259, 1112, 858, 793, 735, 492cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{16}H_{14}FNS$ 271.0830; Found 271.0822.

*5-chloro-9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3fa**)*: Light yellow liquid, PE as the eluent, 47.1 mg, 66% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.3 Hz, 1H), 6.81 – 6.76 (m, 2H), 6.70 (d, *J* = 2.1 Hz, 1H), 6.61 (d, *J* = 8.3 Hz, 1H), 3.51 – 3.47 (m, 2H), 2.59 (t, *J* = 6.1 Hz, 2H), 2.14 (s, 3H), 2.00 (p, *J* = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 141.9, 140.3, 132.1, 128.1, 127.6, 127.2, 126.1, 125.9, 124.6, 121.9, 120.9, 112.7, 46.8, 28.1, 21.6, 20.3; IR (KBr): 2927, 2855, 1561, 1495, 1466, 1318, 1256, 1186, 1090, 1026, 858, 799, 637, 526 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{16}H_{14}ClNS$ 287.0535; Found 287.0524.

*4-bromo-9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ga**)*: Light yellow liquid, PE as the eluent, 44.2 mg, 53% yield; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.95 (dd, *J* = 8.1, 3.2 Hz, 1H), 6.90 – 6.80 (m, 2H), 6.69 (dd, *J* = 8.1, 3.1 Hz, 1H), 6.65 (dd, *J* = 8.6, 3.3 Hz, 1H), 3.63 – 3.50 (m, 2H), 2.69 (q, *J* = 6.1 Hz, 2H), 2.14 (d, *J* = 3.0 Hz, 3H), 2.00 (q, *J* = 4.7, 4.0 Hz, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 143.8, 142.1, 132.3, 128.0, 127.7, 125.8, 125.5, 124.6, 123.9, 122.3, 120.2, 113.1, 46.4, 28.9, 21.4, 20.3; IR (KBr): 2922, 2854, 1552, 1438, 1412, 1255, 1163, 1026, 796, 490 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{16}H_{14}BrNS$ 331.0030; Found 331.0019.

*5-methoxy-9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ha**)*:Light yellow liquid, PE as the eluent, 52.4 mg, 74% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 5.9 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.58 (s, 1H), 6.47 (s, 1H), 3.76 (s, 3H), 3.67 – 3.62 (m, 2H), 2.75 (t, *J* = 5.3 Hz, 2H), 2.27 (s, 3H), 2.14 (p, *J* = 6.0 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 154.6, 142.8, 135.3, 131.3, 127.9, 127.6, 125.9, 121.5, 121.2, 113.3, 112.3, 110.6, 55.6, 46.8, 28.5, 21.8, 20.3; IR (KBr): 2934, 2836, 1602, 1497, 1463, 1430, 1309, 1248, 1135, 1045, 801, 721, 556 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NOS$ 283.1031; Found 283.1021.

4-methoxy-9-methyl-2,3-dihydro-1H-pyrido[3,2,1-

*kl]phenothiazine (**3ia**):* Light yellow liquid, PE as the eluent, 22.5 mg, 32% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.44 (d, *J* = 8.4 Hz, 1H), 3.81 (s, 3H), 3.71 – 3.65 (m, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 2.27 (s, 3H), 2.15 – 2.08 (m, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.7, 142.9, 142.5, 131.6, 127.7, 127.6, 124.5, 122.7, 114.3, 112.8, 112.0, 103.7, 55.6, 46.4, 21.5, 21.0, 20.2; IR (KBr): 2929, 2838, 1579, 1495, 1464, 1426, 1333, 1253, 1196, 1125, 1091, 1065, 1031, 873, 795, 624, 554 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NOS$ 283.1031; Found 283.1023.

*9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine-5-carboxylate (**3ja**):* Yellow liquid, PE/EtOAc (10:1) as the eluent, 23.4 mg, 30% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.54 (s, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 6.90 (s, 1H), 6.75 (d, *J* = 8.2 Hz, 1H), 3.87 (s, 3H), 3.70 – 3.62 (m, 2H), 2.77 (t, *J* = 5.8 Hz, 2H), 2.25 (s, 3H), 2.17 (p, *J* = 5.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 166.6, 145.6, 140.9, 132.9, 129.5, 128.8, 127.6, 126.7, 123.9, 122.8, 121.2, 119.3, 113.1, 51.9, 47.1, 28.1, 21.6, 20.2; IR (KBr): 2945, 2857, 1711, 1594, 1498, 1429, 1322, 1271, 1225, 1188, 1097, 995, 899, 802, 764, 636, 554, 452 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{18}H_{17}NO_2S$ 311.0980; Found 311.0967.

*9-methyl-1,2-dihydro-[1,4]oxazino[2,3,4-kl]phenothiazine (**3ka**):*Green liquid, PE as the eluent, 38.4 mg, 60% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 6.0 Hz, 2H), 6.83 – 6.78 (m, 1H), 6.72 (d, *J* = 7.8 Hz, 2H), 6.65 (d, *J* = 8.5 Hz, 1H), 4.40 (t, *J* = 4.5 Hz, 2H), 3.77 (t, *J* = 4.4 Hz, 2H), 2.27 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 144.8, 140.5, 132.2, 130.8, 128.0, 127.9, 122.5, 120.6, 120.1, 120.0, 115.8, 112.1, 64.0, 45.1, 20.3; IR (KBr): 2921, 2868, 1581, 1496, 1459, 1319, 1260, 1110, 1060, 976, 897, 800, 770, 720, 532, 492, 453 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{15}H_{13}NOS$ 255.0718; Found 255.0708.

*9-methyl-1,2-dihydro-[1,4]thiazino[2,3,4-kl]phenothiazine (**3la**):* Light yellow liquid, PE as the eluent, 31.1 mg, 46% yield ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 2.0 Hz, 1H), 7.00 (d, *J* = 1.5 Hz, 1H), 6.98 (d, *J* = 1.5 Hz, 1H), 6.94 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.84 (t, *J* = 7.7 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 4.20 – 4.13 (m, 2H), 3.26 – 3.17 (m, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 143.4, 138.8, 132.5, 128.0, 126.1, 125.6, 124.0, 123.8, 122.6, 121.4, 112.3, 47.2, 25.2, 20.4; IR (KBr): 3122, 2920, 1733, 1488, 1422, 1244, 1194, 1094, 1045, 801, 762, 605, 491 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{15}H_{13}NS_2$ 271.0489; Found 271.0480.

*3,10-dimethyl-10H-phenothiazine (**3ma**):* Known product,[20] light yellow solid, PE as the eluent, 31.3 mg, 55% yield, m.p: 145-146 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (t, *J* = 8.3 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.95 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 3.38 (s, 3H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 146.1, 143.4, 132.0, 127.9, 127.7, 127.4, 127.2, 123.4, 123.2, 122.2, 113.9, 35.3, 20.4; IR (KBr): 3054, 2915, 2818, 1603, 1571, 1496, 1459, 1327, 1256, 1137, 1036, 837, 810, 753, 490 cm^{-1}; MS (EI), m/z: 227.1 $[M]^+$.

*3-methoxy-7,10-dimethyl-10H-phenothiazine (**3na**):* Brownish solid, PE as the eluent, 34.5 mg, 54% yield, m.p: 105-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 8.6 Hz, 2H), 6.80 (s, 1H), 6.74 (s, 2H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.78 (s, 3H), 3.34 (s, 3H), 2.28 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) : δ 155.2, 143.9, 139.8, 131.6, 128.0, 127.7, 124.7, 122.8, 114.3, 113.6, 112.9, 112.6, 55.8, 35.3, 20.3; IR (KBr): 2952, 2827, 1591, 1502, 1470, 1262, 1225, 1152, 1037, 811, 741, 595, 491 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{15}H_{15}NOS$ 257.0874; Found 257.0865.

*10-butyl-3-methyl-10H-phenothiazine (**3oa**):* Light yellow liquid, PE as the eluent, 27.6 mg, 41% yield, m.p: 134-136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) : δ 7.19 – 7.15 (m, 2H), 7.03 – 6.95 (m, 2H), 6.93 (dd, *J* = 7.4, 1.2 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 8.1 Hz, 1H), 3.95 – 3.81 (m, 2H), 2.28 (s, 3H), 1.86 – 1.77 (m, 2H), 1.49 (h, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 145.7, 142.8, 131.9, 127.9, 127.7, 127.4, 127.1, 124.8, 124.8, 122.0, 115.2, 47.0, 29.1, 20.3, 20.2, 13.9; IR (KBr): 2955, 2924, 2868, 1575, 1494, 1463, 1282, 1241, 1218, 1134, 1039, 806, 744 cm^{-1}; HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{17}H_{20}NS$ 270.1310; Found 270.1307.

*3-(3-methyl-10H-phenothiazin-10-yl)propanenitrile (**3pa**):* Brownish solid, PE/CH_2Cl_2 (2:3) as the eluent, 30.6 mg, 46% yield, m.p: 99-100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 – 7.17 (m, 2H), 7.07 – 6.96 (m, 3H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.75 (d, *J* = 8.1 Hz, 1H), 4.29 – 4.18 (m, 2H), 2.87 – 2.80 (m, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.2, 141.3, 133.2, 128.4, 128.0, 127.9, 127.5, 126.2, 126.0, 123.2, 117.6, 115.2, 115.2, 43.5, 20.4, 16.5; IR (KBr): 2921, 2248, 1601, 1578, 1493, 1463, 1333, 1252, 1198, 1108, 1037, 807, 748, 616, 547cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{16}H_{14}N_2S$ 266.0878; Found 266.0868.

*3-methyl-10-phenyl-10H-phenothiazine (**3qa**):* Yellow solid, PE as the eluent, 32.7 mg, 45% yield, m.p: 108-109 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 7.3 Hz, 1H), 6.76 (s, 1H), 6.74 (d, *J* = 7.7 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.55 (d, *J* = 8.3 Hz, 1H), 6.12 (d, *J* = 8.1 Hz, 1H), 6.02 (d, *J* = 8.3 Hz, 1H), 2.09 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.4, 141.8, 141.3, 132.1, 130.7, 130.6, 127.9, 127.4, 127.2, 126.8, 126.8, 122.3, 120.4, 120.3, 116.2, 116.1, 20.2; IR (KBr): 3059, 2920, 2855, 1584, 1493, 1465, 1305, 1250, 1039, 933, 806, 745, 578 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{19}H_{15}NS$ 289.0925; Found 289.0916.

*2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ab**):* Known product,[21] light yellow liquid, PE as the eluent, 33.6 mg, 56% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 – 7.10 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.91 – 6.80 (m, 3H), 3.76 – 3.66 (m, 2H), 2.79 (t, *J* = 6.0 Hz, 2H), 2.18 (p, *J* = 5.9 Hz, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 144.7, 141.3, 127.9, 127.4, 127.0, 125.3, 125.1, 122.3, 121.9, 121.8, 120.2, 112.8, 47.0, 28.2, 21.8; IR (KBr): 3060, 2930, 2857, 1655, 1579, 1438, 1316, 1184, 1103, 740, 603, 490 cm^{-1}: MS (EI, m/z): 239.1 $[M]^+$.

*9-ethyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ac**):* Brownish liquid, PE as the eluent, 51.3 mg, 77% yield; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, *J* = 6.6 Hz, 2H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 6.81 (dd, *J* = 8.2, 5.3 Hz, 2H), 3.71 – 3.65 (m, 2H), 2.78 (t, *J* = 6.0 Hz, 2H), 2.58 (q, *J* = 7.6 Hz, 2H), 2.22 – 2.13 (m, 2H), 1.24 (t, *J* = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 142.5, 141.5, 138.4, 127.8, 126.7, 126.5, 125.3, 125.2, 124.9, 121.7, 121.6, 120.1, 112.7, 47.0, 28.2, 27.8, 21.8, 15.7; IR (KBr): 2960, 2929, 2863, 1600, 1495, 1447, 1314, 1256, 1187, 1111, 878, 808, 746, 605, 568 cm^{-1}. HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{17}NS$ 267.1082; Found 267.1073.

*9-(4-propylcyclohexyl)-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ad**):*Yellow solid, PE as the eluent, 70.1 mg, 77% yield, m.p: 134-135 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.01 (d, *J* = 7.4 Hz, 2H), 6.96 (d, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 7.3 Hz, 1H), 6.80 (d, *J* = 7.9 Hz, 2H), 3.74 – 3.66 (m, 2H), 2.77

(t, J = 5.9 Hz, 2H), 2.40 (t, J = 12.2 Hz, 1H), 2.17 (q, J = 5.8 Hz, 2H), 1.88 (d, J = 11.2 Hz, 4H), 1.44 – 1.38 (m, 4H), 1.27 – 1.22 (m, 2H), 1.19 – 0.84 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.6, 142.1, 141.5, 127.8, 125.7, 125.4, 125.3, 124.9, 121.6, 121.6, 120.1, 112.6, 47.0, 43.6, 40.0, 37.0, 34.4, 33.6, 28.2, 21.8, 20.08, 14.5; IR (KBr): 2974, 2919, 1494, 1446, 1383, 1314, 1259, 1187, 1088, 1049, 881, 803, 759, 735, 434 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{24}H_{29}NS$ 363.2020; Found 363.2008.

*9-(tert-butyl)-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ae**):* White solid, PE as the eluent, 51.9 mg, 70% yield, m.p: 97-98 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.03 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 7.5 Hz, 1H), 6.72 (d, J = 7.2 Hz, 1H), 6.66 (dd, J = 13.9, 7.8 Hz, 2H), 3.53 (s, 2H), 2.62 (t, J = 6.0 Hz, 2H), 2.06 – 1.97 (m, 2H), 1.18 (s, 9H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 145.4, 142.2, 141.4, 127.8, 125.3, 124.9, 124.2, 121.6, 121.3, 120.1, 112.4, 47.0, 34.1, 31.4, 28.2, 21.8; IR (KBr): 3053, 2955, 2863, 1497, 1446, 1262, 1187, 1112, 878, 806, 763, 602 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{19}H_{21}NS$ 295.1395 Found 295.1386.

*9-pentyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3af**):* Light yellow liquid, PE as the eluent, 51.9 mg, 67% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 6.82 (s, 3H), 6.74 (d, J = 7.4 Hz, 1H), 6.70 – 6.61 (m, 2H), 3.63 – 3.45 (m, 2H), 2.63 (t, J = 6.0 Hz, 2H), 2.39 (t, J = 7.6 Hz, 2H), 2.07 – 1.98 (m, 2H), 1.47 (p, J = 7.5 Hz, 2H), 1.22 (td, J = 16.5, 15.4, 6.5 Hz, 4H), 0.80 (t, J = 6.8 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 141.4, 140.5, 135.9, 126.7, 126.2, 125.9, 124.2, 123.8, 120.6, 120.5, 119.0, 111.5, 45.9, 33.7, 30.3, 30.1, 27.2, 21.5, 20.7, 13.0; IR (KBr): 3053, 2925, 2853, 1589, 1467, 1439, 1307, 1257, 1094, 1019, 805, 740, 700 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{23}NS$ 309.1551; Found 309.1541.

*9-phenyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ag**):* Light yellow liquid, PE as the eluent, 26.5 mg, 34% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.41 (d, J = 7.4 Hz, 2H), 7.28 (t, J = 7.1 Hz, 2H), 7.22 (d, J = 6.8 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.73 (d, J = 9.0 Hz, 2H), 6.66 (t, J = 7.3 Hz, 1H), 3.52 (s, 2H), 2.61 (t, J = 6.0 Hz, 2H), 2.00 (p, J = 5.9 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 143.9, 141.0, 140.0, 135.3, 128.8, 128.0, 127.0, 126.4, 126.0, 125.4, 125.4, 125.2, 122.3, 122.0, 119.8, 113.0, 47.1, 28.2, 21.8; IR (KBr): 3058, 3029, 2932, 2860, 1596, 1447, 1324, 1265, 1187, 1044, 808, 762, 730, 696, 569, 512 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{21}H_{17}NS$ 315.1082; Found 315.1070.

*ethyl 2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine-9 carboxylate (**3ah**)* Yellow liquid, PE/CH_2Cl_2 (1:5) as the eluent, 41.2 mg, 53% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.79 (dd, J = 8.6, 2.0 Hz, 1H), 7.70 (d, J = 2.0 Hz, 1H), 6.89 (dd, J = 7.4, 1.7 Hz, 1H), 6.84 (dd, J = 7.4, 1.6 Hz, 1H), 6.79 (dd, J = 14.0, 8.0 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.71 – 3.60 (m, 2H), 2.73 (t, J = 6.1 Hz, 2H), 2.12 (p, J = 5.9 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 166.0, 148.3, 140.0, 129.5, 128.1, 128.0, 125.5, 125.4, 124.1, 122.7, 121.4, 119.6, 111.9, 60.7, 47.3, 28.1, 21.7, 14.4; IR (KBr): 3059, 2974, 2935, 1708, 1578, 1444, 1395, 1264, 1118, 1023, 900, 763, 575 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{18}H_{17}NO_2S$ 311.0980; Found 311.0970.

*N-(2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazin-9-yl)acetamide (**3ai**)*: Light yellow solid, PE/EtOAc (1:1) as the eluent, 15.6 mg, 21% yield, m.p: 236-237 °C; ^1H NMR (400 MHz, DMSO-d_6): δ 9.85 (s, 1H), 7.43 (s, 1H), 7.31 (s, 1H), 6.90 (d, J = 7.6 Hz, 3H), 6.78 (t, J = 7.5 Hz, 1H), 3.64 – 3.54 (m, 2H), 2.71 (t, J = 5.6 Hz, 2H), 2.05 – 2.02 (m, 5H); $^{13}C\{^1H\}$ NMR (101 MHz, DMSO-d_6): δ 168.4, 141.2, 139.9, 134.8, 128.5, 125.6, 125.3, 122.0, 121.1, 118.8, 118.6, 117.7, 113.7, 46.9, 27.9, 24.4, 21.7; IR (KBr): 3008, 2927, 2849, 1764, 1651, 1581, 1525, 1443, 1309, 1264, 1248, 1183, 1013, 872, 802, 762, 606, 480, 451 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{17}H_{16}N_2OS$ 296.0983; Found 296.0975.

*9-(tert-butyl)-3-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3de**):* Light yellow liquid, PE as the eluent, 62.3 mg, 81% yield; ^1H NMR (400 MHz, $CDCl_3$) : δ 7.20 (d, J = 11.4 Hz, 2H), 6.99 (d, J = 7.4 Hz, 2H), 6.85 (t, J = 7.8 Hz, 2H), 3.71 (q, J = 10.9, 10.1 Hz, 2H), 2.94 (q, J = 6.6 Hz, 1H), 2.22 (dd, J = 10.5, 6.7 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.33 (s, 12H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 145.5, 142.2, 141.1, 129.8, 126.7, 125.3, 124.2, 124.1, 121.7, 121.5, 119.8, 112.5, 43.4, 34.1, 31.4, 31.0, 29.0, 21.5; IR (KBr): 3058, 2958, 1601, 1497, 1470, 1436, 1322, 1271, 1192, 1085, 880, 850, 774, 735, 619, 587, 444 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{23}NS$ 309.1551; Found 309.1542.

*5-methoxy-9-(4-propylcyclohexyl)-2,3-dihydro-1H-pyrido[3,2,1-kl] phenothiazine (**3hd**):* Yellow solid, PE as the eluent, 65.1 mg, 66% yield, m.p: 138-139 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.00 (d, J = 7.3 Hz, 2H), 6.78 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H), 6.46 (d, J = 2.7 Hz, 1H), 3.75 (s, 3H), 3.65 (s, 2H), 2.75 (t, J = 5.7 Hz, 2H), 2.39 (t, J = 12.4 Hz, 1H), 2.14 (p, J = 5.7 Hz, 2H), 1.87 (d, J = 11.2 Hz, 4H), 1.43 – 1.36 (m, 4H), 1.27 – 1.20 (m, 2H), 1.19 – 0.83 (m, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 154.6, 143.1, 141.7, 135.2, 125.9, 125.7, 125.4, 121.6, 121.1, 113.3, 112.3, 110.6, 55.6, 46.8, 43.6, 39.8, 37.0, 34.4, 33.6, 28.5, 21.8, 20.1, 14.5; IR (KBr): 2995, 2949, 2919, 2847, 1600, 1496, 1462, 1434, 1309, 1253, 1210, 1136, 1047, 829, 804, 729, 677, 603, 559, 475 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{25}H_{31}NOS$ 393.2126; Found 393.2114.

*5-chloro-9-pentyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3ff**):* Light yellow liquid, PE as the eluent, 36.3 mg, 42% yield; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (d, J = 8.3 Hz, 1H), 6.95 – 6.89 (m, 2H), 6.84 (s, 1H), 6.77 (d, J = 8.3 Hz, 1H), 3.68 – 3.61 (m, 2H), 2.73 (t, J = 5.9 Hz, 2H), 2.52 (t, J = 7.7 Hz, 2H), 2.14 (p, J = 5.6 Hz, 2H), 1.58 (q, J = 7.3 Hz, 2H), 1.34 (td, J = 13.6, 13.2, 5.8 Hz, 4H), 0.92 (t, J = 6.7 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 142.1, 140.3, 137.4, 127.5, 127.2, 127.0, 126.1, 126.0, 124.6, 121.9, 120.8, 112.7, 46.8, 34.8, 31.4, 31.1, 28.1, 22.6, 21.6, 14.1; IR (KBr): 3019, 2951, 2926, 2854, 1600, 1495, 1448, 1318, 1257, 1186, 1091, 857, 802, 645, 558, 456 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{22}ClNS$ 343.1161; Found 343.1151.

*5-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine (**3bb**):* Red liquid, PE as the eluent, 34.8 mg, 55% yield; ^1H NMR (500 MHz, $CDCl_3$): δ 7.16 – 7.04 (m, 2H), 6.86 (t, J = 7.4 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 6.74 (s, 1H), 6.66 (s, 1H), 3.62 (q, J = 5.3, 3.9 Hz, 2H), 2.70 (t, J = 6.2 Hz, 2H), 2.18 (s, 3H), 2.11 (t, J = 5.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 144.9, 138.8, 131.4, 128.5, 127.3, 127.0, 125.7, 124.9, 122.0, 121.7, 120.0, 112.5, 46.9, 28.1, 21.9, 20.2; IR (KBr): 3057, 3009, 2932, 2850, 1578, 1457, 1322, 1261, 1190, 1043, 851, 744, 561, 454 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd. for $C_{16}H_{15}NS$ 253.0925; Found 253.0918.

*10-phenyl-10H-phenothiazine (**3qb**):* Known product,[13] Yellow solid, PE as the eluent, 22.7 mg, 33% yield, m.p: 89-91 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (t, J = 7.5 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.43 (d, J = 7.7 Hz, 2H), 7.05 (d, J = 7.2 Hz, 2H), 6.86 (p, J = 7.2 Hz, 4H), 6.24 (d, J = 7.8 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.3, 141.0, 130.9, 130.8, 128.2, 126.8,

126.7, 122.5, 120.2, 116.1; IR (KBr): 3059, 2922, 1585, 1489, 1460, 1442, 1302, 1255, 1125, 1042, 741, 705, 629 cm^{-1}; MS (EI, m/z): 275.1 $[M]^+$.

*3-methyl-10-(p-tolyl)-10H-phenothiazine (**3rb**):* Light yellow solid, PE as the eluent, 38.1 mg, 50% yield, m.p: 106-107 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 7.4 Hz, 1H), 6.90 – 6.77 (m, 3H), 6.67 (d, *J* = 8.3 Hz, 1H), 6.24 (d, *J* = 8.0 Hz, 1H), 6.15 (d, *J* = 8.3 Hz, 1H), 2.51 (s, 3H), 2.22 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 144.6, 142.1, 138.4, 138.0, 131.9, 131.4, 130.8, 129.9, 127.3, 127.1, 126.8, 126.7, 124.5, 122.0, 119.8, 119.8, 115.8, 115.7, 21.3, 20.2; IR (KBr): 3027, 2919, 2860, 1576, 1505, 1465, 1305, 1249, 1129, 808, 743, 571 cm^{-1}; HRMS (ESI) m/z: $[M]^+$ Calcd for $C_{20}H_{17}NS$ 303.1082; Found 303.1072.

*Synthesis of 1-(cyclohex-1-en-1-yl)-1,2,3,4-tetrahydroquinoline (**3ab-1**):* The mixture of 1,2,3,4-tetrahydroquinoline **1a** (1.33 g, 10 mmol), cyclohexanone **2b** (4.90 g, 50 mmol), *p*-TSA (0.17 g, 1 mmol), anhydrous Na_2SO_4 (1.0 g) and PhMe (20 mL) was stirred in a 100 mL Schleck tube at 120 °C in an oil bath for 12 h. After cooling down to room temperature, the resulting mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica gel eluting with petroleum ether, **3ab-1** was afforded as a light yellow liquid (14.6 mg). ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.3 Hz, 1H), 6.70 (d, *J* = 7.3 Hz, 1H), 6.49 (t, *J* = 7.4 Hz, 1H), 5.63 (s, 1H), 4.12 (s, 1H), 3.22 (t, *J* = 5.4 Hz, 2H), 2.71 (t, *J* = 6.2 Hz, 2H), 2.10 (d, *J* = 21.7 Hz, 4H), 1.88 – 1.82 (m, 2H), 1.70 – 1.64 (m, 2H), 1.64 – 1.58 (m, 2H); $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 141.3, 136.5, 129.5, 127.9, 126.7, 126.1, 121.1, 116.0, 42.1, 29.5, 27.4, 25.5, 23.2, 22.2, 22.2; IR (KBr): 2923, 2832, 1547, 1488, 1327, 1290, 1088, 973, 697. 680 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{15}H_{20}N$ 214.1590; Found 214.1593.

*Synthesis of 9-methyl-2,3-dihydro-1H-pyrido[3,2,1-kl]phenothiazine 7,7-dioxide (**3aa'**):* The mixture of **3aa** (25.3 mg, 0.1 mmol), *m*-CPBA (51.8mg, 0.3 mmol) and CH_2Cl_2 (2 ml) was stirred in a 50 mL Schleck tube at room temperature overnight. The resulting mixture was concentrated by removing the solvent under vacuum, and the residue was purified by preparative TLC on silica gel eluting with PE/CH_2Cl_2 (1:3), **3aa'** was afforded as a White solid (17.4 mg, 61% yield), m.p: 184-185 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 6.0 Hz, 2H), 7.45 (d, *J* = 8.6 Hz, 1H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 4.10 – 3.92 (m, 2H), 3.05 – 2.92 (m, 2H), 2.45 (s, 3H), 2.30 (q, *J* = 5.6 Hz, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 138.8, 137.6, 134.2, 132.5, 131.8, 126.6, 123.0, 122.2, 121.5, 120.7, 114.3, 47.6, 28.1, 21.5, 20.5. IR (KBr): 3030, 2938, 2252, 1594, 1574, 1472, 1446, 1330, 1237, 1215, 1135, 1021, 913, 629, 586 cm^{-1}. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{16}H_{16}NO_2S$ 286.0896; Found 286.0894.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.XXX.

^1H and ^{13}NMR spectra for the products (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Key Research and Development Program of China (2016YFA0602900), National Natural Science Foundation of China (21971071), Guangdong Province Science Foundation (2017B090903003), and the foundation of the Department of Education of Guangdong Province (2017KZDXM085) for financial support.

REFERENCES

(1) (a) Donnier-Marechal, M.; Larchanche, P. E.; Le Broc, D.; Furman, C.; Carato, P.; Melnyk, P. Carboline- and phenothiazine-derivated heterocycles as potent SIGMA-1 protein ligands. *Eur. J. Med. Chem.* **2015**, *89*, 198–206. (b) Darvesh, S.; Darvesh, K. V.; McDonald, R. S.; Mataija, D.; Walsh, R.; Mothana, S.; Lockridge, O.; Martin, E. Carbamates with differential mechanism of inhibition toward acetylcholinesterase and butyrylcholinesterase. *J. M. Chem.* **2008**, *51*, 4200–4212. (c) Bisi, A.; Meli, M.; Gobbi, S.; Rampa, A.; Tolomeo, M.; Dusonchet, L. Multidrug resistance reverting activity and antitumor profile of newphenothiazine derivatives. *Bioorg. Med. Chem.* **2008**, *16*, 6474–6482. (d) Kubota, K.; Kurebayashi, H.; Miyachi, H.; Tobe, M.; Onishi, M.; Isobe, Y. Synthesis and structure–activity relationships of phenothiazine carboxylic acids having pyrimidine-dione as novel histamine H1 antagonists. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2766–2771. (e) Pluta, K.; Jelen, M.; Morak-Mlodawska, B.; Zimecki, M.; Artym, J.; Kocieba, M.; Zaczynska, E. Azaphenothiazines-promising phenothiazine derivatives. An insight into nomenclature, synthesis, structure elucidation and biological properties. *Eur. J. Med. Chem.* **2017**, *138*, 774–806. (f) Jelen, M.; Bavavea, E. I.; Pappa, M.;

Kourounakis, A. P.; Morak-Mlodawska, B.; Pluta, K. Synthesis of quinoline/naphthalene-containing azaphenothiazines and their potent in vitro antioxidant properties. *Med. Chem. Res.* **2015**, *24*, 1725–1732.
(2) (a) Motarojas, D.; Orozcogregorio, H.; Gonzalezlozano, M.; Roldansantiago, P. Therapeutic approaches in animals to reduce the impact of stress during transport to the slaughterhouse: a review. *Int. J. Pharm.* **2011**, *7,* 568–578. (b) Persona, K.; Madej, K.; Knihnicki, P.; Piekoszewski, W. Analytical methodologies for the determination of benzodiazepines in biological samples. *J. Pharm. Biomed. Anal.* **2015**, *113*, 239–264. (c) Liu, C.; Shen, Y.; Yuan, K. Non-directed copper-catalyzed regioselective C–H sulfonylation of phenothiazines. *Org. Biomol. Chem.* **2019**, *17*, 5009–5013.
(3) (a) Chao, P.; Gu, R.; Ma, X.; Wang, T.; Zhao, Y. Thiophene-substituted phenothiazine-based photosensitisers for radical and cationic photopolymerization reactions under visible laser beams (405 and 455 nm). *Polym. Chem.* **2016**, *7*, 5147–5156. (b) Chen, Y.; Kuo, Y.; Liang, C.-J. Numbers of cyanovinyl substitutes and their effect on phenothiazine based organic dyes for dyesensitized solar cells. *RSC Adv.* **2018**, *8*, 9783–9789. (c) Quinton, C.; Sicard, L.; Vanthuyne, N.; Jeannin, O.; Poriel, C. Confning nitrogen inversion to yield enantiopure quinolino[3,2,1-k]phenothiazine Derivatives. *Adv. Funct. Mater.* **2018**, *28,* 183140. (d) Poriel, C.; Rault-Berthelot, J.; Thiery, S.; Quinton, C.; Jeannin, O.; Biapo, U.; Tondelier, D.; Geffroy, B. 9H-Quinolino[3,2,1-k]phenothiazine: a new electron-rich fragment for organic electronics. *Chem. Eur. J.* **2016**, *22*, 17930–17935. (e) Bae, J.; McNamara, L. E.; Nael, M. A.; Mahdi, F.; Doerksen, R. J.; Bidwell, G. L.; Hammer, N. I.; Jo, S. Nitroreductase-triggered activation of a novel caged fluorescent probe obtained from methylene blue. *Chem. Commun.* **2015**, *51*, 12787–12790. (f) Buene, A. F.; Ose, E. E.; Zakariassen, A. G.; Hagfeldt, A.; Hoff, B. H. Auxiliary donors for phenothiazine sensitizers for dye-sensitized solar cells – how important are they really. *J. Mater. Chem. A* **2019**, *7*, 7581–7590. (g) Liu, F.; Du, J.; Song, D.; Xu, M.; Sun, G. A sensitive fluorescent sensor for the detection of endogenous hydroxyl radicals in living cells and bacteria and direct imaging with respect to its ecotoxicity in living zebra fish. *Chem. Commun.* **2016**, *52*, 4636–4639.
(4) (a) Zhou, M.; Chen, Y.; Zhang, Q.; Xi, Y.; Yu, J.; Du, Y.; Hu, Y.; Wang, Q. Na3V2(PO4)3 as the sole solid energy storage material for redox flow sodium-ion battery. *Adv. Energy Mater.* **2019**, *9*, 1901188. (b) Xing, X.; Liu, Q.; Li, J.; Han, Z.; Wang, B.; Lemmon, J. P. A nonaqueous all organic semisolid flow battery. *Chem. Commun.,* **2019**, *55*, 14214–14217. (c) Engelhardt, F.; Spielmann, W.; Bremer, C.; Obermiiller, A.; Christian, J. Stabilized aqueous polym er com positions and their use. Patent, EP2166060, **2010**. (d) Sorensen, N. H.; McDevitt, J. P. Method for treating hair. Patent, US6572843, **2003**.
(5) Dahl, T.; Tornøe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jørgensen, M. Palladium-catalyzed three-component approach to promazine with formation of one carbon–sulfur and two carbon–nitrogen bonds. *Angew. Chem. Int. Ed.* **2008**, *47*, 1726–1728.
(6) (a) Ma, D.; Geng, Q.; Zhang, H.; Jiang, Y. Assembly of substituted phenothiazines by a sequentially controlled CuI/L-proline-catalyzed cascade C-S and C-N bond formation. *Angew. Chem. Int. Ed.* **2010**, *49*, 1291–1294. (b) Tang, J.; Xu, B.; Mao, X.; Yang, H.; Wang, X.; Lv, X. One-pot synthesis of pyrrolo[3,2,1-kl]phenothiazines through copper-catalyzed tandem coupling/double cyclization reaction. *J. Org. Chem.* **2015**, *80*, 11108–11114.
(7) (a) Dai, C.; Sun, X.; Tu, X.; Wu, L.; Zhan, D.; Zeng, Q. Synthesis of phenothiazines via ligand-free CuI-catalyzed cascade C–S and C–N coupling of aryl ortho-dihalides and ortho-aminobenzenethiols. *Chem. Commun.* **2012**, *48*, 5367–5369. (b) Hu, W.; Zhang, S. Method for the synthesis of phenothiazines via a domino iron-catalyzed C-S/C-N cross-coupling reaction. *J. Org. Chem.* **2015**, *80*, 6128-6132. (c) Huang, M.; Huang, D.; Zhu, X.; Wan, Y. Copper-catalyzed domino reactions for the synthesis of phenothiazines. *Eur. J. Org. Chem.* **2015**, 4835–4839.
(8) (a) Chen, J.; Li, G.; Xie, Y.; Liao, Y.; Xiao, F.; Deng, G.-J. Four-component approach to N-substituted phenothiazines under transition-metal-free conditions. *Org. Lett.* **2015**, *17*, 5870–5873. (b) Liao, Y.; Jiang, P.; Chen, S.; Xiao, F.; Deng, G.-J. Synthesis of phenothiazines from cyclohexanones and 2-aminobenzenethiols under transition-metal-free conditions. *RSC Adv.* **2013**, *3*, 18605.
(9) (a) Xie, R.; Xie, F.; Zhou, C. J.; Jiang, H.; Zhang, M. Hydrogen transfer-mediated selective dual C–H alkylations of 2-alkylquinolines by doped TiO2-supported nanocobalt oxides. *J. Catal.* **2019**, *377*, 449–454. (b) Xie, F.; Lu, G.-P.; Xie, R.; Chen, Q.-H.; Jiang, H.-F.; Zhang, M. MOF-derived subnanometer cobalt catalyst for selective C-H oxidative sulfonylation of tetrahydroquinoxalines with sodium sulfonates. *ACS Catal.* **2019**, *9*, 2718–2724. (c) Xie, F.; Chen, Q.-H.; Xie, R.; Jiang, H.-F.; Zhang, M. MOF-derived nanocobalt for oxidative functionalization of cyclic amines to quinazolinones with 2-aminoarylmethanols. *ACS Catal.* **2018**, *8*, 5869–5874. (d) Chen, X. W.; Zhao, H.; Chen, C. L.; Jiang, H. F.; Zhang, M. Hydrogen transfer-mediated α-functionalization of 1,8-naphthyridines by a strategy overcoming the over-Hydrogenation barrier. *Angew. Chem. Int. Ed.* **2017**, *56*, 14232–14236. (e) Liang, T.; Zhao, H.; Gong, L.; Jiang, H.; Zhang, M. Direct access to functionalized indoles via single electron oxidation induced coupling of diarylamines with 1,3-dicarbonyl compounds. *Org. Lett.* **2019**, *21*, 6736–6740. (f) Tan, Z.; Liang, Y.; Yang, J.; Cao, L.; Jiang, H.; Zhang, M. Site-specific oxidative C-H chalcogenation of (hetero)aryl-fused cyclic amines enabled by nanocobalt oxides. *Org. Lett.* **2018**, *20*, 6554–6558.
(10) (a) Wang, H.; Li, Y.; Lu, Q.; Yu, M.; Bai, X.; Wang, S.; Cong, H.; Zhang, H.; Lei, A. Oxidation-induced β-Selective C-H bond functionalization: thiolation and selenation of N-heterocycles. *ACS Catal.* **2019**, *9*, 1888–1894. (b) Xiao, F.; Xie, H.; Liu, S.; Deng, G.-J. Iodine-catalyzed regioselective sulfenylation of indoles with sodium sulfinates. *Adv. Synth. Catal.* **2014**, *356*, 364–368. (c) Wang, M.; Fan, Q.; Jiang, X. Transition-metal-free diarylannulated sulfide and selenide construction via radical/anion-mediated sulfur-iodine and selenium-iodine exchange. *Org. Lett.* **2016**, *18*, 5756–5759. (d) Xu, Z.; Deng, G.; Zhang, F.; Chen, H.; Huang, H. Three-component cascade bis-heteroannulation of aryl or vinyl methylketoxime acetates toward thieno[3,2-c]isoquinolines. *Org. Lett.* **2019**, *21*, 8630–8634. (e) Che, X.; Jiang, J.; Xiao, F.; Huang, H.; Deng, G. Assembly of 2-arylbenzothiazoles through three-component oxidative annulation under transition-metal-free Conditions. *Org. Lett.* **2017**, *19*, 4576–4579. (f) Li, G.; Xie, H.; Chen, J.; Guo, Y.; Deng, G. Three-component synthesis of 2-heteroarylbenzothiazoles under metal-free conditions. *Green Chem.* **2017**, *19*, 4043. (g) Xu, Z.; Huang, H.; Chen, H.; Deng, G. Catalyst- and additive-free annulation/aromatization leading to benzothiazoles and naphthothiazoles. *Org. Chem. Front.* **2019**, *6*, 3060–3064.
(11) (a) Tan, Z.; Jiang, H.; Zhang, M. A novel iridium/acid co-catalyzed transfer hydrogenative C(sp3)–H bond alkylation to access functionalized N-heteroaromatics. *Chem. Commun.* **2016**, *52*, 9359–9362. (b) Xie, R.; Xie, F.; Zhou, C.-J.; Jiang, H.-F.; Zhang, M. Hydrogen transfer-mediated selective dual C–H alkylations of 2-alkylquinolines by doped TiO2-supported nanocobalt oxides. *J. Catal.* **2019**, *377*, 449–454.
(12) (a) Jansen, A.; Pauluth, D.; Klasen-Memmer, M. 2,5-selenophene derivatives and 2,5-tellurophene derivatives. Patent, US8304036, **2012**. (b) Sucrow, W.; Radecker, G. Bi- and tercyclohexylderivate durch Claisen-Umlagerung. *Chem. Ber.* **1988**, *121*, 219-224.
(13) (a) Narupai, B.; Page, Z. A.; Treat, N. J.; McGrath, A. J.; Pester, C. W.; Discekici, E. H.; Dolinski, N. D.; Meyers, G. F.; Read de Alaniz, J.; Hawker, C. J. Simultaneous preparation of multiple polymer brushes under ambient conditions using microliter volumes. *Angew. Chem. Int. Ed.* **2018**, *57*, 13433–13438. (b) Discekici, E. H.; Pester, C. W.; Treat, N. J.; Lawrence, J.; Mattson, K. M.; Narupai, B.; Toumayan, E. P.; Luo, Y.; McGrath, A. J.; Clark, P. G.; Read de Alaniz, J.; Hawker, C. J. Simple benchtop approach to polymer brush nanostructures using visible-light-mediated metal-free atom transfer radical polymerization. *ACS Macro. Lett.* **2016**, *5*, 258–262.
(14) (a) Discekici, E. H.; Treat, N. J.; Poelma, S. O.; Mattson, K. M.; Hudson, Z. M.; Luo, Y.; Hawker, C. J.; de Alaniz, J. R. A highly reducing metal-free photoredox catalyst: design and application in radical dehalogenations. *Chem. Commun.* **2015**, *51*, 11705–11708. (b) Wang, H.; Jui, N. T. Catalytic defluoroalkylation of trifluoromethylaromatics with unactivated alkenes. *J. Am. Chem. Soc.* **2018**, *140*, 163–166.
(15) (a) Chen, S. H.; Li, Y. P.; Wang, M.; Jiang, X. F. General sulfone construction via sulfur dioxide surrogate control. *Green. Chem.* **2020**, *22*, 322–326. (b) Zhang J.; Yang, M.; Liu, J. B.; He, F. S.; Wu, J. A copper-catalyzed insertion of sulfur dioxide via radical coupling. *Chem.*

Commun. **2020**, DOI: 10.1039/d0cc00375a. (c) Wang, X. F.; Kuang, Y. Y.; Ye, S. Q.; Wu, J. Photoredox-catalyzed synthesis of sulfones through deaminative insertion of sulfur dioxide. *Chem. Commun.* **2019**, 55, 14962–14964. (d) Li, Y.; Rizvi, A.; Hu, D.; Sun, D.; Gao, A.; Zhou, Y.; Li, J.; Jiang, X. Selective late-stage oxygenation of sulfides with ground-state oxygen by uranyl photocatalysis. *Angew. Chem. Int. Ed.* **2019**, *58*, 13499–13506. (e) Ishihara, T.; Kakuta, H.; Moritani, H.; Ugawa, T.; Yanagisawa, I. Synthesis and biological evaluation of quinuclidine derivatives incorporating phenothiazine moieties as squalene synthase inhibitors. *Chem. Pharm. Bull.* **2004**, *52,* 1204–1209. (f) Kalgutkar, A.; Gardner, I.; Obach, R.; Shaffer, C.; Callegari, E.; Henne, K.; Mutlib, A.; Dalvie, D.; Lee, J.; Nakai, Y.; O'Donnell, J.; Boer, J.; Harriman, S. A comprehensive listing of bioactivation pathways of organic functional groups. *Curr. Drug Metab.* **2005**, *6*,161–225.

(16) (a) Gu, Z. Y.; Cao, J. J.; Wang, S. Y.; Ji, S. J. The involvement of the trisulfur radical anion in electron-catalyzed sulfur insertion reactions: facile synthesis of benzothiazine derivatives under transition metal-free conditions. *Chem. Sci.* **2016**, *7*, 4067–4072. (b) Li, J. H.; Huang, Q.; Wang, S. Y.; Ji, S. J. Trisulfur radical anion (S3•-) involved [1 + 2 + 2] and [1 + 3 + 1] cycloaddition with aromatic alkynes: synthesis of tetraphenylthiophene and 2-benzylidenetetrahydrothiophene Derivatives. *Org. Lett.* **2018**, *20*, 4704–4708. (c) Zhang, G.; Yi, H.; Chen, H.; Bian, C.; Liu, C.; Lei, A. Trisulfur radical anion as the key intermediate for the synthesis of thiophene via the interaction between elemental Ssulfur and NaOtBu. *Org. Lett.* **2014**, *16*, 6156–6159.

(17) (a) Stavber, G.; Iskra, J.; Zupan, M.; Stavber, S. Aerobic oxidative iodination of ketones catalysed by sodium nitrite "on water" or in a micelle-based aqueous system. *Green Chem.* **2009**, *11*, 1262–1267. (b) Stavber, S.; Jereb, M.; Zupan, M. Selectfluor™ F-TEDA-BF4 mediated and solvent directed iodination of aryl alkyl ketones using elemental iodine. *Chem. Commun.* **2002**, 488–489.

(18) Zhou, P.; Huang, Y.; Wu, W.; Zhou, J.; Yu, W.; Jiang, H. Access to 2-aroylthienothiazoles via C-H/N-O bond functionalization of oximes. *Org. Lett.* **2019**, *21*, 9976–9980.

(19) (a) Rueping, M., Theissmann, T., Antonchick, A. P. Metal-free brønsted acid catalyzed transfer hydrogenation-new organocatalytic reduction of quinolines. *Synlett*, **2006**, 1071-1074. (b) Chen, S. J., Lu, G. P., Cai, C. Synthesis of quinolines from allylic alcohols via iridium-catalyzed tandem isomerization/cyclization combined with potassium hydroxide. *Synthesis*, **2015**, *47*, 976-984.

(20) Ebdrup, S. Preparation of 3-substituted 10-methylphenothiazines. *J. Chem. Soc., Perkin Trans. 1,* **1998**, 1147-1150.

(21) Catsoulacos, P., Catsoulacos, D. On the synthesis of pyrido [3, 2, 1-kl] phenothiazine, quino [8, 1-bc][1, 4] benzothiazepine and their derivatives. *Journal of heterocyclic chemistry*, **1992**, *29*, 675-682.