Copper(II) Triflate Promoted One-Pot Synthesis of Coumarin-, Quinolone-, and Naphthalene-Annulated 2-Aminothiazoles under Ligand-Free Conditions

K. C. Majumdar,*[a,b] Nirupam De,[a] Debankan Ghosh,[a] Sudipta Ponra,[a] B. Roy[a]

[a] Department of Chemistry, University of Kalyani, Kalyani 741235, W.B., India

[b] Department of Chemical Sciences, Tezpur University, Napaam 784028, Assam, India
E-mail: kcm_ku@yahoo.co.in

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Abstract: An efficient synthesis of new 2-aminothiazole-annulated compounds is described via copper(II) triflate promoted sequential condensation, arylation, and heterocyclization reactions in one step. The reaction is compatible with a variety of substrates providing efficient access to many biologically important skeletons in good yields.

Key words: copper triflate, multicomponent reaction, naphthothiazole, domino synthesis, carbon disulfide

Heterocyclic compounds are important structural units useful in medicinal chemistry and valuable as synthetic organic building blocks. Among the various heterocycles, the 2-aminothiazole subunit has great pharmaceutical importance due to its presence (annulated with other carbo- and heterocycles) in a broad range of natural and synthetic compounds of biological interest.[1–3] For example, coumarin- and quinolone-annulated 2-aminothiazole compounds can act as effective anti-inflammatory and analgesic agents,[4] naphthothiazole-based mono-methine cyanine dye is used as an effective staining tool for the visualization of macromolecules such as DNA,[5] and naphthothiazole-containing carboxamides can act as novel antitumor agents and DNA photocleavers.[6] Both compounds **I** and **II** (Figure 1) showed potent anticonvulsant activity.[7,8]

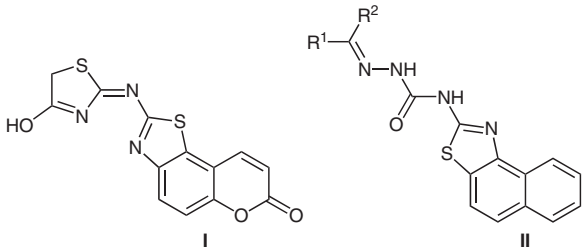

Figure 1 2-Aminochromenothiazole and 2-aminonaphthothiazole derivatives: anticonvulsant agents

In most methods reported so far for the synthesis of 2-aminothiazole-annulated compounds, phenylureas have been frequently used as key intermediates and harmful bromine has been used for cyclization.[9,10] Recently, some metal-catalyzed methods have been developed for their synthesis, but most require either expensive catalytic systems or a variety of ligands or complex precursors not easy to synthesize.[11,12] In some reports the amino group was introduced at the 2-position of the benzothiazole moiety in a separate step.[13] Thus, the synthesis of coumarin-, quinolone-, and naphthalene-annulated 2-aminothiazoles by a simple, step-economic, less hazardous methodology is still outstanding. In recent years, there has been increased attention in the design and implementation of multicomponent reactions (MCR) for the construction of diverse heterocyclic scaffolds, as these fulfill present-day requirements, such as the use of simple and readily available starting materials and step- and atom-economic synthesis involving minimal human resource, energy etc.[14] In this context, in continuation our interest in the synthesis of bioactive heterocyclic scaffolds,[15] we undertook a study to synthesize important scaffolds, carbo- and heterocycle-annulated 2-aminothiazoles, via a copper(II) triflate promoted MCR approach. Herein we report our results.

Most recently, Ma et al. described the copper(II) chloride catalyzed domino synthesis of 2-aminobenzothiazoles.[16] To explore the scope of this methodology in achieving our target compounds we started with the reaction of 6-amino-5-bromocoumarin (**1a**) with carbon disulfide and pyrrolidine using copper(II) chloride dihydrate. Unfortunately, the desired coupling product, coumarin-annulated 2-aminothiazoles **4a**, was obtained in poor yield (only 21%). We envisioned that a ligand might be necessary to improve the yield of the reaction. We then tried the reaction using L-proline or 1,10-phenanthroline as ligands in separate experiments, but no improvement of the yield was observed. We, therefore, modified the reaction conditions by changing the copper salts through a series of experiments (Table 1). After several attempts, the reaction afforded the desired product **4a** in 81% yield using copper(II) triflate (1.0 equiv) and potassium carbonate (3.0 equiv) at 120 °C in *N*,*N*-dimethylformamide (entry 6). It was also found that the concentration of copper(II) triflate may be reduced to 0.5 equivalents without affecting yield of the product. Other copper sources such as copper(I) chloride, bromide, or iodide were found to be less effective (entries 2–4). The reaction failed completely when copper(II) acetate was used (entry 5). Further screening of bases did not improve the efficiency of this reaction (entries 11 and 12). The coupling product was also formed without using any base, but in trace amounts. Among several solvents

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N,*N*-dimethylformamide was found to be superior to dimethylacetamide and dimethyl sulfoxide while acetonitrile and toluene were found to be ineffective (entry 6 vs. entries 7–10).

Table 1 Optimization of the Reaction Conditions[a]

Entry	Promoter[b]	Solvent	Base	Yield[c] (%)
1	$CuCl_2 \cdot 2H_2O$	DMF	K_2CO_3	21[d]
2	CuCl	DMF	K_2CO_3	15
3	CuBr	DMF	K_2CO_3	18
4	CuI	DMF	K_2CO_3	trace
5	$Cu(OAc)_2$	DMF	K_2CO_3	0
6	$Cu(OTf)_2$[e]	DMF	K_2CO_3	81
7	$Cu(OTf)_2$	MeCN[f]	K_2CO_3	0
8	$Cu(OTf)_2$	DMA	K_2CO_3	58
9	$Cu(OTf)_2$	toluene	K_2CO_3	0
10	$Cu(OTf)_2$	DMSO	K_2CO_3	35
11	$Cu(OTf)_2$	DMF	Cs_2CO_3	72
12	$Cu(OTf)_2$	DMF	Na_2CO_3	40

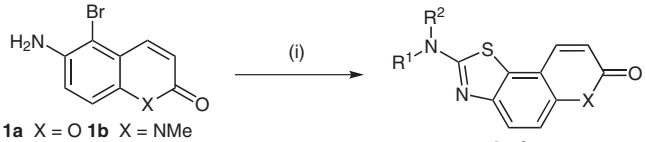
[a] Reaction conditions: **1a** (1.0 mmol), pyrrolidine (1.5 mmol), CS_2 (1.2 mmol), base (3.0 mmol), Cu salt (1.0 mmol), anhyd solvent (5 mL), 120 °C, 8 h.
[b] Unless otherwise stated promoter (1.0 equiv) was used.
[c] Isolated yield.
[d] Results using entry 1 with various ligands are not shown.
[e] Promoter (0.5 equiv) was used.
[f] Reflux temperature.

With the optimized conditions in hand, the scope of this methodology was extended to different amine sources and other heterocyclic systems. The results show that the precursors **1a–c** successfully gave the desired 2-aminothiazole derivatives **4a–j** in good yields (Table 2). It was also found that 3-amino-4-iodocoumarin (**1d**) reacted smoothly to afford the cyclized products **4k–l** in high yields (Table 3).

Encouraged by these results, we next chose naphthalene systems as precursors. Both 1-amino-2-bromonaphthalene (**1e**) and 2-amino-1-bromonaphthalene (**1f**) afforded the 2-aminothiazole derivatives **4m–o** in moderate yields. Thus, the same protocol also worked well for naphthalene systems in addition to heterocyclic systems (Table 4).

The formation of the products **4** has been rationalized by the initial formation of dithiocarbamic acids[17] by the reaction of carbon disulfide with the amine. Such acids are very unstable, so they instantly react with potassium carbonate forming dithiocarbamate salts[18] which in turn undergo Ullmann-type coupling reaction with the *o*-haloamine-annulated compounds in the presence of copper(II) triflate promoter to afford the dithiocarbamate **2**. It is noteworthy that the reaction occurs in the absence of a ligand although a ligand is usually required for such type

Table 2 7*H*-Chromeno[6,5-*d*][1,3]thiazoles and [1,3]Thiazolo[5,4-*f*]quinolines by Annulation of 6-Amino-5-bromo-substituted Quinolones and Coumarins[a]



1a X = O **1b** X = NMe
1c X = NEt

4a–j

Entry	Product	Yield (%)
1	**4a**	81
2	**4b**	74
3	**4c**	65
4	**4d**	83
5	**4e**	75
6	**4f**	69
7	**4g**	78
8	**4h**	81
9	**4i**	86
10	**4j**	81

[a] Reaction conditions: (i) **1a–c** (1.0 mmol), CS_2 (1.2 mmol), amine (1.5 mmol), K_2CO_3 (3.0 mmol), $Cu(OTf)_2$ (0.5 mmol), anhyd DMF (5 mL), 120 °C, 6–9 h.

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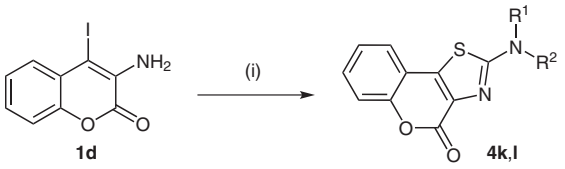
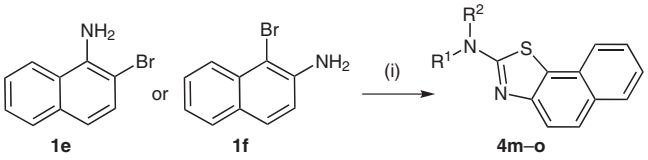
Table 3 4*H*-Chromeno[3,4-*d*][1,3]thiazoles by Annulation of a 3-Amino-4-iodo-substituted Coumarin[a]



Entry	Product	Yield (%)
1	**4k**	80
2	**4l**	83

[a] Reaction conditions: (i) **1d** (1.0 mmol), CS_2 (1.2 mmol), amine (1.5 mmol), K_2CO_3 (3.0 mmol), $Cu(OTf)_2$ (0.5 mmol), anhyd DMF (5 mL), 120 °C, 6 h.

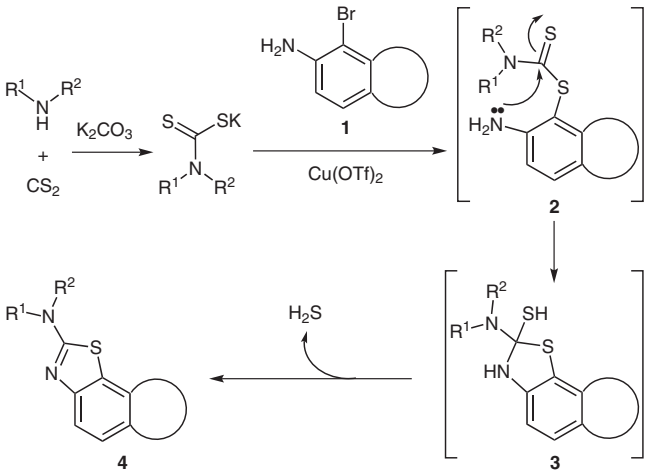
Table 4 Naphtho[1,2-*d*][1,3]thiazoles and Naphtho[2,1-*d*][1,3]thiazoles by Annulation of 1-Amino-2-bromo- and 2-Amino-1-bromonaphthalenes[a]



Entry	Product	Yield (%)
1	**4m**	49
2	**4n**	77
3	**4o**	80

[a] Reaction conditions: (i) **1e/1f** (1.0 mmol), CS_2 (1.2 mmol), amine (1.5 mmol), K_2CO_3 (3.0 mmol), $Cu(OTf)_2$ (0.5 mmol), anhyd DMF (5 mL), 120 °C, 6–7 h.

of coupling. The cyclization may occurs by the nucleophilic attack of the amino group of **2** to the C=S bond to form the cyclic intermediates **3**, which on subsequent elimination of hydrogen sulfide may finally give the desired cyclic products **4** (Scheme 1).



Scheme 1 Probable mechanistic route

In summary, we have developed a convenient and efficient protocol that provides an easy access to a variety of coumarin-, quinolone- and naphthalene-annulated 2-aminothiazoles in good yields from simple starting materials. Closely related analogues of the synthesized compounds[4–8] possess potential bioactivity. The methodology is step economic and less hazardous. The synthesized compounds with the synthetic strategy as well would be useful to the pharmacologists and medicinal chemists.

All chemicals were procured from either Sigma Aldrich Chemicals Pvt. Ltd. or Spectrochem, India. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrophotometer on KBr disks. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ with TMS as internal standard. CHN was recorded on a Perkin-Elmer 2400 series II CHN analyzer. MS(ESI) were recorded on a Q-TOF micro instrument. HRMS(ESI) were recorded on a QTOF MicroYA 263. Silica gel [(60–120, 230–400 mesh), Rankem, India] was used for chromatographic separation. Silica gel (GF-254) was used for TLC. Petroleum ether (PE) has bp 60–80 °C.

2-Pyrrolidin-1-yl-7*H*-chromeno[6,5-*d*][1,3]thiazol-7-one (4a); Typical Procedure

A mixture of CS_2 (1.2 mmol), pyrrolidine (1.5 mmol), and K_2CO_3 (3 mmol) was stirred in DMF (5 mL) at r.t. for 10 min. Then 6-amino-5-bromocoumarin **1a** (1 mmol) and $Cu(OTf)_2$ (0.5 mmol) were added to the solution. The mixture was then heated with stirring at 120 °C for 8 h. The solution was allowed to cool to r.t., and partitioned between EtOAc and H_2O. The organic layer was collected, washed with H_2O and brine, and dried (Na_2SO_4). The solvent was removed under reduced pressure to give a crude mass, which was purified by column chromatography (silica gel) to afford **4a** as a green solid; yield: 220 mg (81%); mp 256–258 °C.

IR (KBr): 1550, 1622, 1712, 2872 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (br s, 4 H), 3.60 (br s, 4 H), 6.49 (d, *J* = 9.6 Hz, 1 H), 7.29 (d, *J* = 9.2 Hz, 1 H), 7.69 (d, *J* = 9.2 Hz, 1 H), 7.71 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 49.8, 112.7, 115.1, 116.7, 121.8, 128.0, 141.0, 149.1, 150.3, 160.8, 164.7.

MS (ESI): *m*/*z* = 273.00 $[M + H]^+$.

Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.58; H, 4.51; N, 10.41.

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Compound 4b
Greenish yellow solid; yield: 212 mg (74%); mp 140–142 °C.

IR (KBr): 1540, 1618, 1722, 2860 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.72 (br s, 6 H), 3.62 (br s, 4 H), 6.47 (d, *J* = 9.6 Hz, 1 H), 7.25 (d, *J* = 8.8 Hz, 1 H), 7.63 (d, *J* = 8.8 Hz, 1 H), 7.69 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 25.3, 49.8, 112.6, 114.9, 116.6, 121.9, 127.9, 140.9, 149.2, 149.9, 160.8, 168.3.

MS (ESI): *m*/*z* = 287.06 $[M + H]^+$, 309.04 $[M + Na]^+$.

Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 63.03; H, 4.99; N, 9.62.

Compound 4c
Brown solid; yield: 196 mg (65%); mp 144–146 °C.

IR (KBr): 1545, 1619, 1730, 2873 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 12 H), 3.96–3.99 (m, 2 H), 6.45 (d, *J* = 9.6 Hz, 1 H), 7.23 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 9.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 51.4, 112.4, 114.6, 116.4, 121.8, 127.2, 141.3, 148.9, 150.3, 160.9, 164.9.

MS (ESI): *m*/*z* = 303.05 $[M + H]^+$, 325.02 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.55; H, 6.00; N, 9.26. Found: C, 63.74; H, 5.89; N, 9.17.

Compound 4d
Greenish yellow solid; yield: 267 mg (83%); mp 198–200 °C.

IR (KBr): 1534, 1619, 1723, 2870 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, *J* = 7.2 Hz, 3 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 6.40 (d, *J* = 9.6 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1 H), 7.40 (d, *J* = 7.6 Hz, 2 H), 7.45 (m, 1 H), 7.52 (d, *J* = 7.6 Hz, 2 H), 7.56 (d, *J* = 9.6 Hz, 1 H), 7.71 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 47.9, 112.4, 114.9, 116.6, 122.1, 127.9, 128.4, 128.5, 130.3, 140.9, 143.7, 149.5, 149.8, 160.7, 167.7.

MS (ESI): *m*/*z* = 323.01 $[M + H]^+$, 345.00 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.13; H, 4.27; N, 8.76.

Compound 4e
Greenish yellow solid; yield: 264 mg (75%); mp 192–194 °C.

IR (KBr): 1533, 1607, 1714, 2856 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.0 Hz, 3 H), 3.88 (s, 3 H), 4.06 (q, *J* = 7.0 Hz, 2 H), 6.40 (d, *J* = 9.6 Hz, 1 H), 7.03 (d, *J* = 8.8 Hz, 2 H), 7.25 (d, *J* = 8.8 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 2 H), 7.55 (d, *J* = 9.6 Hz, 1 H), 7.69 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.1, 47.8, 55.6, 112.4, 114.8, 115.5, 116.5, 122.0, 128.6, 129.6, 136.4, 140.9, 149.4, 150.0, 159.6, 160.7, 168.6.

MS (ESI): *m*/*z* = 352.97 $[M + H]^+$, 374.95 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{16}N_2O_3S$: C, 64.76; H, 4.58; N, 7.95. Found: C, 64.59; H, 4.61; N, 8.07.

Compound 4f
Yellow solid; yield: 217 mg (69%); mp 154–156 °C.

IR (KBr): 1545, 1612, 1662, 2883 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 12 H), 3.76 (s, 3 H), 3.98–4.02 (m, 2 H), 6.76 (d, *J* = 9.6 Hz, 1 H), 7.29 (d, *J* = 9.2 Hz, 1 H), 7.68 (d, *J* = 9.6 Hz, 1 H), 7.70 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.3, 29.9, 51.1, 112.3, 114.3, 121.3, 121.8, 128.2, 134.6, 136.1, 148.7, 161.8, 164.7.

MS (ESI): *m*/*z* = 316.07 $[M + H]^+$, 338.05 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{21}N_3OS$: C, 64.73; H, 6.71; N, 13.32. Found: C, 64.91; H, 6.62; N, 13.27.

Compound 4g
Greenish yellow solid; yield: 233 mg (78%); mp 166–168 °C.

IR (KBr): 1538, 1612, 1645, 2855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.72 (br s, 6 H), 3.63 (br s, 4 H), 3.76 (s, 3 H), 6.78 (d, *J* = 9.6 Hz, 1 H), 7.32 (d, *J* = 8.8 Hz, 1 H), 7.67 (d, *J* = 9.6 Hz, 1 H), 7.73 (d, *J* = 8.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 25.3, 29.9, 49.8, 112.8, 114.5, 121.3, 122.0, 129.8, 135.2, 136.0, 148.2, 161.6, 164.5.

MS (ESI): *m*/*z* = 300.04 $[M + H]^+$, 322.03 $[M + Na]^+$.

Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04. Found: C, 64.33; H, 5.73; N, 13.95.

Compound 4h
Yellow solid; yield: 271 mg (81%); mp 142–144 °C.

IR (KBr): 1542, 1614, 1654, 2865 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 3.75 (s, 3 H), 4.12 (q, *J* = 7.2 Hz, 2 H), 6.69 (d, *J* = 9.2 Hz, 1 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.40–7.45 (m, 3 H), 7.49–7.54(m, 3 H), 7.77 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 29.9, 47.8, 112.7, 114.3, 121.6, 121.9, 127.9, 128.3, 129.5, 130.3, 135.5, 135.8, 143.9, 148.2, 161.8, 167.5.

MS (ESI): *m*/*z* = 336.00 $[M + H]^+$, 357.97 $[M + Na]^+$.

Anal. Calcd for $C_{19}H_{17}N_3OS$: C, 68.03; H, 5.11; N, 12.53. Found: C, 68.22; H, 5.02; N, 12.49.

Compound 4i
Yellow solid; yield: 269 mg (86%); mp 176–178 °C.

IR (KBr): 1535, 1614, 1651, 2855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.38 (t, *J* = 7.2 Hz, 3 H), 1.72 (br s, 6 H), 3.63 (br s, 4 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 6.76 (d, *J* = 9.6 Hz, 1 H), 7.34 (d, *J* = 9.2 Hz, 1 H), 7.65 (d, *J* = 9.6 Hz, 1 H), 7.71 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 24.2, 25.3, 37.7, 49.8, 112.6, 114.7, 121.4, 122.1, 129.1, 134.1, 135.8, 148.1, 161.3, 165.2.

MS (ESI): *m*/*z* = 314.08 $[M + H]^+$, 336.06 $[M + Na]^+$.

Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41. Found: C, 65.06; H, 6.15; N, 13.47.

Compound 4j
Green solid; yield: 242 mg (81%); mp 234–236 °C.

IR (KBr): 1542, 1618, 1661, 2855 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.2 Hz, 3 H), 2.10–2.13 (m, 4 H), 3.61 (t, *J* = 6.4 Hz, 4 H), 4.41 (q, *J* = 7.2 Hz, 2 H), 6.76 (d, *J* = 9.6 Hz, 1 H), 7.35 (d, *J* = 9.2 Hz, 1 H), 7.67 (d, *J* = 9.6 Hz, 1 H), 7.77 (d, *J* = 9.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.9, 25.7, 37.7, 49.7, 112.7, 114.8, 121.3, 122.0, 129.0, 133.9, 135.9, 148.5, 161.3, 164.5.

HRMS (TOF, ES^+): *m*/*z* $[M + Na]^+$ calcd for $C_{16}H_{17}N_3NaOS$: 322.0990; found: 322.0995.

Compound 4k
Brown solid; yield: 218 mg (80%); mp 246–248 °C.

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IR (KBr): 1559, 1602, 1723, 2852 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.12 (br s, 4 H), 3.61 (br s, 4 H), 7.27–7.37 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 50.2, 116.8, 117.0, 123.5, 124.6, 128.5, 135.0, 137.9, 150.2, 156.0, 165.5.

MS (ESI): *m/z* = 272.98 $[M + H]^+$, 294.94 $[M + Na]^+$.

Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.87; H, 4.38; N, 10.23.

Compound 4l
Brown solid; yield: 267 mg (83%); mp 180–182 °C.

IR (KBr): 1538, 1604, 1733, 2872 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.2 Hz, 3 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 7.18–7.24 (m, 2 H), 7.37–7.41 (m, 4 H), 7.46 (t, *J* = 7.6 Hz, 1 H), 7.54 (t, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 47.9, 116.5, 117.2, 123.7, 124.6, 127.7, 128.8, 128.9, 130.7, 135.9, 137.3, 143.7, 150.6, 155.9, 169.0.

MS (ESI): *m/z* = 323.04 $[M + H]^+$, 345.01 $[M + Na]^+$.

Anal. Calcd for $C_{18}H_{14}N_2O_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 66.91; H, 4.44; N, 8.62.

Compound 4m
Off-white solid; yield: 124 mg (49%); mp 79–81 °C.

IR (KBr): 1555, 1622, 2853 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 2.11 (br s, 4 H), 3.70 (br s, 4 H), 7.46–7.62 (m, 3 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.86 (d, *J* = 8.4 Hz, 1 H), 8.71 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 48.5, 117.8, 119.7, 123.0, 124.0, 124.1, 124.5, 125.7, 126.8, 131.1, 148.1, 164.9.

MS (ESI): *m/z* = 255.04 $[M + H]^+$.

Anal. Calcd for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01. Found: C, 70.64; H, 5.56; N, 11.13.

Compound 4n
Off-white solid; yield: 206 mg (77%); mp 90–92 °C.

IR (KBr): 1541, 1616, 2850 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.72–1.77 (m, 6 H), 3.65–3.67 (m, 4 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 7.49 (t, *J* = 8.0 Hz, 1 H), 7.69–7.74 (m, 3 H), 7.87 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.2, 25.3, 49.7, 119.6, 123.6, 123.7, 124.9, 126.5, 126.6, 128.2, 128.9, 129.3, 150.8, 169.4.

MS (ESI): *m/z* = 269.07 $[M + H]^+$.

Anal. Calcd for $C_{16}H_{16}N_2S$: C, 71.61; H, 6.01; N, 10.44. Found: C, 71.76; H, 6.08; N, 10.51.

Compound 4o
Gummy mass; yield: 243 mg (80%).

IR (KBr): 1529, 1612, 2852 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, *J* = 7.2 Hz, 3 H), 4.16 (q, *J* = 7.2 Hz, 2 H), 7.34 (t, *J* = 7.2 Hz, 1 H), 7.39–7.45 (m, 4 H), 7.51 (t, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 1 H), 7.71–7.78 (m, 2 H), 7.84 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.2, 30.9, 47.7, 119.7, 123.7, 123.8, 125.4, 126.4, 126.5, 127.8, 128.0, 128.8, 129.5, 130.2, 144.3, 150.5, 168.5.

MS (ESI): *m/z* = 305.03 $[M + H]^+$.

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