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Synthesis and biological evaluation of (*R*)-*N*-(diarylmethylthio/sulfinyl)ethyl/propyl-piperidine-3-carboxylic acid hydrochlorides as novel GABA uptake inhibitors

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Abstract—A series of new (*R*)-1-(2-diarylmethylthio/sulfinyl) ethyl-piperidine-3-carboxylic acid hydrochlorides **5a–d/6a–d** and (*R*)-1-(3-diarylmethylthio) propyl-piperidine-3-carboxylic acid hydrochlorides **5′a–d** were synthesized and evaluated as γ-aminobutyric acid uptake inhibitors through cultured cell lines expressing mouse GAT1. Biological screening results demonstrated that the compounds **6a–d** with diarylmethylsulfinyl ethyl side chain show more potent GAT-1 inhibitory activities than **5a–d/5′a–d** with diarylmethylthio ethyl/propyl moieties. Some of them, such as **6a**, exhibited excellent inhibitions of [^{3}H]-GABA uptake in cultured cells, which is 496-fold higher than (*R*)-nipecotic acid and 11.5 times less than tiagabine. The synthesis and structure–activity relationships are discussed.

γ-Aminobutyric acid (GABA) is referred to the major inhibitory neurotransmitter in the central nervous system (CNS). Dysfunctioning of GABAergic synapses resulting in a decrease of GABAergic transmission causes the diseases such as epilepsy, Parkinson's disease, Huntington's chorea, and some forms of schizophrenia. Therefore, enhancement of GABA transmission by inhibition of GABA uptake has drawn attention as a therapeutic strategy, and GABA transporters (GATs) are regarded as the main functional components of regulating GABA transmission in the CNS.[1–3] So far, four different subtypes of GABA transporters (GAT1–GAT4) have been cloned. GAT1 is deemed to be the predominant neuronal transmitter transporter in the rodent brain in the study of pharmacologic criteria and immunohistochemical localization.[4,5] GABA uptake inhibitors have been proved effective as anticonvulsants in a variety of experimental models of epilepsy or in epileptic patients.

Several cyclic amino acids and their derivatives are regarded as effective inhibitors of GAT1, such as (*R*)-nipecotic acid (**1**), guvacine (**2**), and (*R*)-tiagabine[6,7] (**3**) (Fig. 1). (*R*)-Tiagabine has been employed as an antiepileptic drug in clinic.[8,9]

A new model of ligand interaction at GAT1 uptake site was brought forward by Andersen et al. in 1999. This new model postulated interaction of an electronegative region in the GABA uptake inhibitor with a positively charged domain in the protein structure of the GAT-1 site. Further work indicated that this electronegative moiety is part of the linker in GABA uptake inhibitors.[10] The increasing electronegative character of the linker can increase inhibitory activities of GABA uptake inhibitors in vitro.[11] For example, diarylvinyl functions of (*R*)-tiagabine can be regarded as the electronegative region of GABA uptake inhibitors. A series of *N*-(benzhydrol ethyl) of nipecotic acid analogues were explored[12] and found that several compounds exhibited potent inhibitory activities for GABA uptake in vitro. The benzhydrol ethyl-containing side chains also can be deemed to be the electronegative area. According to this new model and to our study on GABA uptake inhibitors,[13] a series of new (*R*)-1-(2-diarylmethylthio/sulfinyl)ethyl-piperidine-3-carboxylic acid hydrochlorides **5a–d/6a–d** and (*R*)-1-(3-diarylmethylthio/

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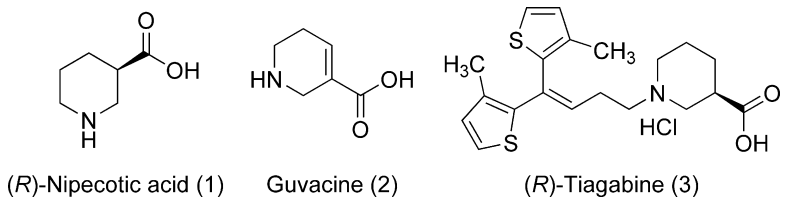

Figure 1. Structure of typical GABA uptake inhibition.

sulfinyl)propyl-piperidine-3-carboxylic acid hydrochlorides **5′a–d** were designed and synthesized by our team (Fig. 2). Diarylmethylthio moieties of **5a–d/5′a–d** could be deemed to replace diarylvinyl functions of tiagabine as the electronegative region of GABA uptake inhibitor. In order to increase electronegative character, **6a–d** were synthesized by using diarylmethylsulfinyl groups instead of diarylmethylthio moieties of **5a–d**. The racemic compound of structure **5a** had been tested for GABA uptake inhibition in rat hippocampus slices.[12,14]

The synthetic routes of the target compounds **5a–d/6a–d** and **5′a–d** are shown in Figure 2. According to general procedure, the starting material **1a–d** was obtained easily by treatment of the substituted aryl aldehyde with the substituted aryl bromide through Grignard reaction. The key intermediates **2a–d** were thereby synthesized by S-alkylation method by treatment of various benzhydrol derivatives **1a–d** with 2-mercaptoethanol in the presence of trifluoroacetic acid.[15] However, under this condition, no other than the corresponding trifluoroacetic ester of **2a–d** could be obtained. As a result, the compounds **2a–d** could be prepared by reacting the above obtained ester with K_2CO_3 and a little water at room temperature in good yields. **2′a–d** were also prepared by treatment of **1a–d** with 3-mercaptopropanol in TFA and then with K_2CO_3 and a little water. Then, **2a–d** or **2′a–d** were converted into the corresponding

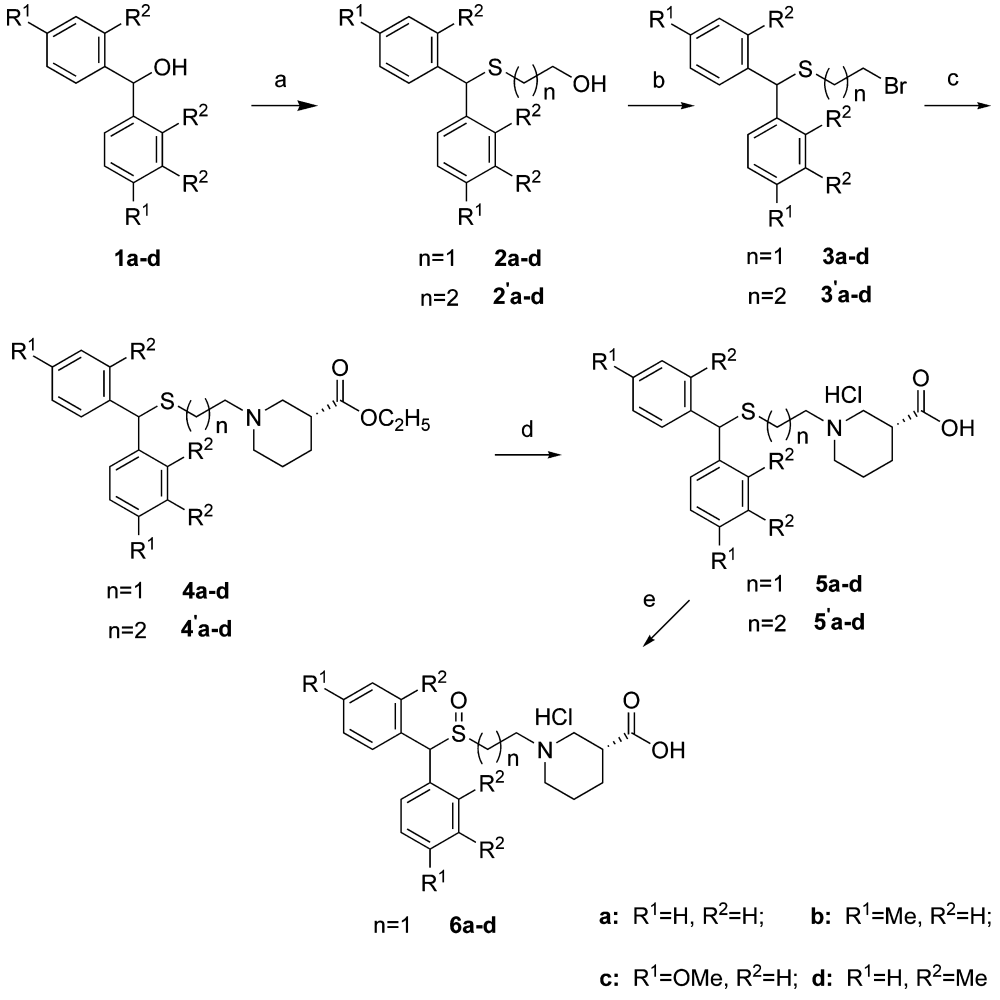

Figure 2. Reagents and conditions: (a) $HSCH_2CH_2OH$ or $HSCH_2CH_2CH_2OH$, TFA, 0 °C, rt; K_2CO_3, H_2O; (b) Ph_3P, CBr_4, imidazole, CH_2Cl_2, 0 °C, rt; (c) (*R*)-3-ethyl-piperidinecarboxylate, Kl, K_2CO_3, acetone, rt; (d) 12 N NaOH, 4 N HCl, EtOH, rt; (e) 30% H_2O_2, CH_3OH, rt.

diarylmethyl-(2-bromoethyl)sulfane **3a–d** or diarylmethyl-(3-bromopropyl)sulfane **3′a–d** via halogenation reaction. First, this conversion was conducted by treatment of **2a–d** or **2′a–d** with hydrogen bromide or phosphorus tribromide, resulting in poor yields due to side-products. Subsequently, **3a–d** or **3′a–d** could be prepared by treatment of **2a–d** or **2′a–d** with triphenylphosphine and carbon tetrabromide. However, it was hard to separate the products **3a–d** or **3′a–d** with the residual triphenylphosphine owing to the similar polarity. By overcoming this problem, the obtained crude products **3a–d** or **3′a–d** were directly used in the next step without separation. Treatment of the crude **3a–d** or **3′a–d** with (*R*)-3-ethyl-piperidinecarboxylate gave (*R*)-ethyl-1-(2-diarylmethyl-thio)ethyl-piperidine-3-carboxylate **4a–d** or (*R*)-ethyl-1-(3-diarylmethylthio)propyl-piperidine-3-carboxylate **4′a–d** in good yield. Whereafter, upon saponification, acidification of **4a–d** or **4′a–d** yielded the target compounds (*R*)-1-(2-diarylmethylthio)ethyl-piperidine-3-carboxylic acid hydrochlorides **5a–d** or (*R*)-1-(3-diarylmethylthio)propyl-piperidine-3-carboxylic acid hydrochlorides **5′a–d**. Finally, **5a–d** were oxidized tenderly with 30% H_2O_2 to provide other target compounds (*R*)-1-(2-diarylmethylsulfinyl)ethyl-piperidine-3-carboxylic acid hydrochlorides **6a–d**. The overall yields of **5a–d** by using this method were from 36% to 56% and the yields of **5′a–d** were in the range of 44–56%. The overall yields of **6a**, **6b**, **6c**, and **6d** are 29%, 38%, 40%, and 38%, respectively. The yields, melting points, and $[\alpha]_D^{25}$ of compounds **4a–d**, **4′a–d**, **5a–d**, **5′a–d**, and **6a–d** are listed in Table 1. General procedures for the preparation of the target compounds **6a–d** could be found in note.[16] The spectral data for compounds **4a–d**, **4′a–d**, **5a–d**, **5′a–d** and **6a–d** could also be seen in the reference.[19–23] Compounds **5a–d**, **5′a–d**, and **6a–d** were investigated as inhibitors of GABA transporters on cultured cell lines expressing mouse GAT1 in transport assay.[17,18] (*R*)-Nipecotic acid (**1**) and (*R*)-tiagabine (**3**) were employed for comparison. In order to elucidate the functional roles of chemical moieties, the intermediates **4a–d** and **4′a–d** were also tested in the same manner. The IC_{50} values for GABA uptake in vitro are also summarized in Table 1. The IC_{50} values show that the N-alkylated amino acid ester derivatives **4a–d** and **4′a–d** are almost inactive. However, when ester moieties are replaced by the carboxylic groups to form the N-alkylated amino acid derivatives **5a–d** and **5′a–d**, **5a–d** exhibit similar activity compared to (*R*)-nipecotic acid (**1**), and **5′a–d** have 15- to 100-fold higher potency than **5a–d** (entries **9–12** vs **13–16**), indicating that the free carboxyl of nipecotic plays the very important role for the inhibitory activities. Besides, elongation of the chain in compounds **5′a–d** leads to improved potency for GAT1. Surprisingly, compounds **6a–d** with diarylmethylsulfinyl groups exhibit more potent inhibitory effect than compounds **5a–d** and **5′a–d** with diarylmethylthio moieties, which implies that employment of diarylmethylsulfinyl groups instead of diarylmethylthio moieties can increase electronegative character and affect the binding of compound to GAT1 at the uptake site. Compounds **6a** and **6b** exhibit excellent inhibitions of [^{3}H]-GABA uptake in cultured cells. Especially, **6a** shows higher inhibitory activity than (*R*)-nipecotic acid 496 times and less than (*R*)-tiagabine 11.5 times. On the other hand, compounds **6a** and **6b** possess greater potency than **6c** and **6d** owing to different alkyl substituents which presumably have a limiting effect on the possible coplanarity of the two aryl moieties as a result of steric repulsion. With the aim to identify GABA uptake inhibitors with improved pharmacological properties, further studies on the steric and electronic properties of the aryl and heteroaryl moieties are in progress and the results will be published later.

Table 1. The yields, melting point, $[\alpha]_D^{25}$, and IC_{50} of compounds **4a–d**, **4′a–d**, **5a–d**, **5′a–d**, and **6a–d**

Entry	Compound	Yield (%)	Mp (°C)	$[\alpha]_D^{25}$	IC_{50} (μM)
1	**4a**	55[a]	Oil	−19.9 (c 1.00)[b]	—
2	**4b**	68[a]	Oil	−16.0 (c 1.20)[b]	—
3	**4c**	81[a]	Oil	−14.8 (c 0.45)[b]	—
4	**4d**	85[a]	Oil	−18.6 (c 1.40)[b]	—
5	**4′a**	55[a]	Oil	−11.9 (c 1.70)[b]	—
6	**4′b**	56[a]	Oil	−15.7 (c 1.20)[b]	—
7	**4′c**	59[a]	Oil	−14.1 (c 1.74)[b]	—
8	**4′d**	89[a]	Oil	−12.0 (c 0.70)[b]	—
9	**5a**	36	98–100	−5.0 (c 1.20)[c]	1600
10	**5b**	49	94–96	−5.3 (c 1.00)[c]	240
11	**5c**	47	100–102	−7.1 (c 0.65)[c]	4800
12	**5d**	56	116–118	−5.5 (c 1.10)[c]	2130
13	**5′a**	51	182–184	−6.8 (c 1.20)[c]	11.60
14	**5′b**	44	120–122	−6.2 (c 1.35)[c]	15.80
15	**5′c**	48	148–150	−3.2 (c 1.00)[c]	120
16	**5′d**	56	158–160	−4.3 (c 0.85)[c]	16.90
17	**6a**	29	78–80		0.92
18	**6b**	38	Gum		1.18
19	**6c**	40	Gum		589
20	**6d**	38	86–88		105
21	**1**				456
22	**3**				0.08

[a] The yields of **4a–d** or **4′a–d** are yields of two steps.
[b] The determining solvent of **4a–d** or **4′a–d** is $CHCl_3$.
[c] The determining solvent of **5a–d** or **5′a–d** is CH_3OH.

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16. General procedures for the preparation of the target compounds **6a**–**d** were as follows:
    To a solution of **1a**–**d** (8.14 mmol) and mercaptoethanol (20.70 mmol) in dry CH_2Cl_2 (10 mL) was added TFA (3.40 mL, 30 mmol) and then stirred at rt for 2 h. The solvent and TFA were removed in vacuo. The residues were dissolved in acetone and K_2CO_3 (8.14 mmol) and a little water were added in. The mixture was kept stirring overnight. To the mixture water (20 mL) was added and extracted with CH_2Cl_2, washed, dried, and concentrated. The residues were subjected to column separation over silica gel to give **2a**–**d** (79–96%) in oil form.
    To a solution of **2a**–**d** (3.33 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C were added triphenylphosphine (13.31 mmol), imidazole (16.64 mmol), and carbon tetrabromide (5.00 mmol), and stirred at rt for 6 h. Following the general disposal procedure, crude products **3a**–**d** were provided and could be directly used in the next step without separation.
    The compounds **3a**–**d** (2.24 mmol) were dissolved in acetone (10 mL), and (*R*)-3-ethyl-piperidinecarboxylate (2.24 mmol), potassium iodide (0.22 mmol), and K_2CO_3 (2.24 mmol) were added and stirred at rt for 48 h. Following to the general disposal procedure, **4a**–**d** were obtained (55–85%, two steps) as a gum.
    To a solution of **4a**–**d** (3.2 mmol) in ethanol (10 mL) was added 12 mol/L aqueous NaOH (0.5 mL) and stirred at rt for 4 h. The mixture was cooled to 0 °C and the pH was adjusted to 1–2 with 4 mol/L aqueous HCl. CH_2Cl_2 (20 mL) was added and the phases were separated. The organic phase was washed with water (5 mL) and dried. After removal of the solvent in vacuo, the solid residue was recrystallized from ethyl acetate and hexane to provide compounds **5a**–**d** (69–82%) as solid.
    To a solution of **5a**–**d** (1.28 mmol) in methanol (10 mL) was added 30% H_2O_2 (0.3 mL) and stirred at rt overnight. Saturated aqueous $Na_2S_2O_3$ was added and stirred for 1 h. The organic phase was extracted with CH_2Cl_2, washed, dried, and concentrated. The residues were separated on a silica gel column to give **6a**–**d** (75–85%).
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18. General procedure of bioassay: D8 cells, in RMPI1640 medium (Gibco-BRL Life Technologies) containing 10% FBS (Gibco-BRL Life Technologies), were grown to near confluence in 48-well tissue culture plates (Costar) (approximately 60,000 cells per well), rinsed with phosphate-buffered saline (PBS), and pre-incubated in 100 μL Hanks′-balanced salt solution (HBSS) for 10 min at rt [^{3}H]-GABA (Amersham Pharmacia Biotech) was added to final concentrations of 151 nM. The cells were incubated for 20 min at rt. The reaction was terminated by aspiration of the HBSS and the cells were washed three times rapidly (10 s/wash) with cold PBS. The cells were then solubilized in 2 N NaOH and an aliquot was measured by liquid scintillation counting (Beckman LS 5000 TA) to quantify the uptake of [^{3}H]-GABA. Inhibition studies were performed by addition of the inhibitor at the beginning of the transport assay and IC_{50} values were measured by linear regression analysis.
19. *Data for compounds* **4a**–**d**.
    Compound **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.24 (t, 3H, J = 7.2 Hz, —$COOCH_2CH_3$), 1.37–1.41 (m, 1H), 1.50–1.54 (m, 1H), 1.64–1.69 (m, 1H), 1.89–1.96 (m, 2H), 2.06–2.16 (m, 1H), 2.50–2.58 (m, 5H), 2.65–2.69 (m, 1H), 2.88–2.91 (m, 1H), 4.07–4.14 (q, 2H, J = 6.9 Hz, —$COOCH_2$—), 5.21 (s, 1H, —CHS—), 7.18–7.43 (m, 10H, ArH); ESIMS (*m*/*z*): 384 $(M+H)^+$. HRMS (ESI): Calcd for $C_{23}H_{29}NO_2S$ + H: 384.1990460, found: 384.1991763.
    Compound **4b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.20 (t, 3H, J = 7.8 Hz, —$COOCH_2CH_3$), 1.27–1.37 (m, 1H), 1.48–1.55 (m, 1H), 1.66–1.74 (m, 2H), 1.90–1.97 (m, 2H), 2.06–2.13 (m, 1H), 2.30 (s, 6H, —CH_3Ph), 2.48–2.53 (m, 4H), 2.67–2.70 (m, 1H), 2.89–2.93 (m, 1H), 4.07–4.14 (q, 2H, J = 6.9 Hz, —$COOCH_2$—), 5.14 (s, 1H, —CHS—), 7.10 (d, 4H, J = 7.8 Hz, PhH), 7.30 (d, 4H, J = 8.4 Hz, PhH); ESIMS (*m*/*z*): 412$(M+H)^+$. HRMS (ESI): Calcd for $C_{25}H_{33}NO_2S$ + H: 412.2306470, found: 412.2304765.
    Compound **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.24 (t, 3H, J = 7.2 Hz, —$COOCH_2CH_3$), 1.37–1.67 (m, 3H), 1.89–1.98(m, 2H), 2.06–2.10 (m, 1H), 2.47–2.57(m, 5H), 2.66–2.69 (m, 1H), 2.89–2.92 (m, 1H), 3.75 (s, 6H, —OCH_3), 4.07–4.14 (q, 2H, J = 6.9 Hz, —$COOCH_2$—), 5.14 (s, 1H, —CHS—), 6.83 (d, 4H, J = 8.7 Hz, PhH), 7.32 (d, 4H, J = 8.4 Hz, PhH); ESIMS (*m*/*z*): 444 $(M+H)^+$. HRMS (ESI): Calcd for $C_{25}H_{33}NO_4S$: 444.2206830, found: 444.2203057.
    Compound **4d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.24 (t, 3H, J = 7.2 Hz, —$COOCH_2CH_3$), 1.31–1.40 (m, 1H), 1.46–1.58 (m, 1H), 1.60–1.66 (m, 1H), 1.89–1.95 (m, 2H), 2.07–2.11 (m, 1H), 2.23 (s, 3H, —CH_3), 2.28 (s, 3H, —CH_3), 2.32 (s, 3H, —CH_3), 2.51–2.59 (m, 5H), 2.69–2.76 (m, 1H), 2.87–2.98 (m, 1H),4.07–4.14 (q, 2H, J = 7.2 Hz, —$COOCH_2$—), 5.54 (s, 1H, —CHS—), 7.04–7.06 (m, 2H, PhH), 7.12–7.17 (m, 3H, PhH), 7.31–7.33 (m, 1H, PhH), 7.45–7.48 (m, 1H, PhH); ESIMS (*m*/*z*): 426 $(M+H)^+$. HRMS (ESI): Calcd for $C_{26}H_{35}NO_2S$ + H: 426.2466620, found: 426.2461265.
20. *Data for compounds* **4′a**–**d**.
    Compound **4′a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.23 (t, 3H, J = 6.9 Hz, —$COOCH_2CH_3$), 1.39–1.52 (m, 2H), 1.65–1.77 (m, 3H), 1.88–1.95 (m, 2H), 2.05–2.13 (m, 1H), 2.33–2.42 (m, 4H), 2.47–2.51 (m, 1H), 2.64–2.68 (m, 1H), 2.88–2.91 (m, 1H), 4.07–4.15 (q, 2H, J = 7.2 Hz, —$COOCH_2$—), 5.15 (s, 1H, —CHS—), 7.17–7.43 (m, 10H, PhH); ESIMS (*m*/*z*): 398 $(M+H)^+$. HRMS (ESI): Calcd for $C_{24}H_{31}NO_2S$ + H: 398.2147710, found: 398.2148264.

Compound **4′b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.25 (t, 3H, J = 7.5 Hz, —$COOCH_2CH_3$), 1.39–1.54 (m, 2H), 1.58–1.70 (m, 4H), 1.89–1.93 (m, 2H), 2.06–2.13 (m, 1H), 2.30 (s, 6H, —CH_3Ph), 2.34–2.41 (m, 3H), 2.47–2.50 (m, 1H), 2.51–2.69 (m, 1H), 2.90–2.94 (m, 1H), 4.09–4.17 (q, 2H, J = 7.2 Hz, —$COOCH_2$—), 5.10 (s, 1H, —CHS—), 7.10 (d, 4H, J = 7.2 Hz, PhH), 7.30 (d, 4H, J = 8.4 Hz, PhH); ESIMS (*m*/*z*): 426 $(M+H)^+$. HRMS (ESI): Calcd for $C_{26}H_{35}NO_2S$ + H: 426.2464260, found: 426.2461265.
Compound **4′c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.23 (t, 3H, J = 6.9 Hz, —$COOCH_2CH_3$), 1.38–1.54 (m, 2H), 1.66–1.77 (m, 3H), 1.89–2.04 (m, 2H), 2.06–2.13 (m, 1H), 2.34–2.39 (m, 4H), 2.48–2.52 (m, 1H), 2.67–2.71 (m, 1H), 2.90–2.94 (m, 1H), 3.77 (s, 6H, -OCH_3), 4.08–4.15 (q, 2H, J = 6.9 Hz, —$COOCH_2$—), 5.09 (s, 1H, —CHS—), 6.83 (d, 4H, J = 7.8 Hz, PhH), 7.31 (d, 4H, J = 8.4 Hz, PhH); ESIMS (*m*/*z*): 458 $(M+H)^+$. HRMS (ESI): Calcd for $C_{26}H_{35}NO_4S$ + H: 458.2366, found: 458.23596.
Compound **4′d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.24 (t, 3H, J = 7.2 Hz, —$COOCH_2CH_3$), 1.47–1.59 (m, 2H), 1.65–1.79 (m, 3H), 1.91–2.01 (m, 2H), 2.15–2.20 (m, 1H), 2.22 (s, 3H, —CH_3), 2.78 (s, 3H, —CH_3), 2.33 (s, 3H, —CH_3),2.37–2.42 (m, 5H), 2.66–2.69 (m, 1H), 2.90–2.93 (m, 1H), 4.08–4.15 (q, 2H, J = 7.2 Hz, —$COOCH_2$—), 5.46 (s, 1H, —CHS—), 7.12–7.14 (m, 2H, PhH), 7.17–7.33 (m, 3H, PhH), 7.34–7.35 (m, 1H, PhH), 7.45–7.48 (m, 1H, PhH); ESIMS (*m*/*z*): 440 $(M+H)^+$. HRMS (ESI): Calcd for $C_{27}H_{37}NO_2S$ + H: 440.2619260, found: 440.2617766.

21. *Data for compounds* **5a**–**d**.
Compound **5a** ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.54–1.67 (m, 2H), 1.93–1.99 (m, 1H), 2.05–2.21(m, 2H), 2.40–2.78 (m, 1H), 2.79–2.96 (m, 1H), 3.09–3.31(m, 5H), 3.39–3.78 (m, 1H), 5.61 (s, 1H, —CHS—), 7.25–7.31(m, 2H), 7.33–7.36 (m, 4H), 7.64–7.66 (m, 4H); ESIMS (*m*/*z*): 390 $(M-H)^-$, 354 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{21}H_{26}ClNO_2S$ – H: 390.1289890, found: 390.1289039.
Compound **5b**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.23–1.25 (m,1H), 1.28–1.39 (m,1H), 1.80–1.84 (m, 1H), 2.05–2.20 (m, 2H), 2.25 (s, 6H, —CH_3Ph), 2.36–2.44 (m, 1H), 2.61–2.79 (m, 1H), 2.85–2.98 (m, 3H), 3.01–3.19 (m, 2H), 3.57–3.60 (m, 1H), 5.18 (s, 1H, —CHS—), 7.11 (d, 4H, J = 8.1 Hz, PhH), 7.30 (d, 4H, J = 8.1 Hz, PhH); ESIMS (*m*/*z*): 418 $(M-H)^-$, 382 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{23}H_{30}ClNO_2S$ – H: 418.1614230, found: 418.1613012.
Compound **5c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.59–1.71 (m, 2H), 2.18–2.24 (m, 2H), 2.37–2.55 (m, 1H), 2.87–2.93 (m, 1H), 3.08–3.28 (m, 6H), 3.48–3.59 (m, 1H), 3.64 (s, 6H, —OCH_3), 5.57 (s, 1H, —CHS—), 7.00 (d, 4H, J = 8.1 Hz, PhH), 7.60 (d, 4H, J = 9.0 Hz, PhH); ESIMS (*m*/*z*): 450 $(M-H)^-$, 414 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{23}H_{30}ClNO_4S$ – H: 450.15130, found: 450.15113.
Compound **5d**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.58–1.66 (m, 2H), 1.99–2.10 (m, 1H), 2.13 (s, 3H, —CH_3Ph), 2.16–2.22 (m, 1H), 2.34 (s, 3H, —CH_3Ph), 2.35–2.39 (m, 1H), 2.42 (s, 3H, —CH_3Ph), 2.79–2.91 (m, 1H), 3.08–3.18 (m, 5H), 3.35–3.43 (m, 1H), 3.63–3.71 (m, 1H), 5.94 (s, 1H, —CHS—), 7.08–7.15 (m, 2H, PhH), 7.26–7.33 (m, 4H, PhH), 7.71–7.32 (m, 1H, PhH); ESIMS (*m*/*z*): 432 $(M-H)^-$, 397 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{24}H_{32}ClNO_2S$ – H: 432.17739, found: 432.17695.

22. *Data for compounds* **5′a**–**d**.
Compound **5′a**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.62–1.72 (m, 2H), 2.22–2.36 (m, 3H), 2.44–2.52 (m, 3H), 2.60–2.68 (m, 1H), 3.00–3.08 (m,1H), 3.15–3.20 (m, 2H), 3.39–3.43 (m, 1H), 3.77–3.85 (m, 1H), 3.90–3.94 (m, 1H), 5.99 (s, 1H, —CHS—), 7.23–7.26 (m, 1H, PhH), 7.32–7.38 (m, 5H, PhH), 7.82–7.85 (m, 4H, PhH); ESIMS (*m*/*z*): 404 $(M-H)^-$, 368 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{22}H_{28}ClNO_2S$ – H: 404.1444070, found: 404.1445539.
Compound **5′b**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.58–1.73 (m, 2H), 1.89–1.97 (m, 1H), 2.19 (s, 6H, —CH_3Ph), 2.26–2.33 (m, 3H), 2.51–2.55 (m, 2H), 2.62–2.70 (m, 1H), 3.01–3.09 (m, 1H), 3.16–3.21 (m, 2H), 3.40–3.44 (m, 1H), 3.78–3.93 (m, 2H), 5.85 (s, 1H, —CHS—), 7.15 (d, 4H, J = 7.8 Hz, PhH), 7.70 (d, 4H, J = 7.8 Hz, PhH); ESIMS (*m*/*z*): 432 $(M-H)^-$, 396 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{24}H_{32}ClNO_2S$ – H: 432.1765460, found: 432.1769512.
Compound **5′c**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.39–1.52 (m, 1H), 1.84–1.88 (m, 1H), 1.94–2.01 (m, 2H), 2.12–2.22 (m, 1H), 2.29–2.44 (m, 2H), 2.51–2.57(m, 1H), 2.96–3.09 (m, 2H), 3.26–3.45 (m, 2H), 3.65–3.70 (m, 1H), 3.77 (s, 6H, —OCH_3), 4.16–4.33 (m, 2H), 5.20 (s, 1H, —CHS—), 6.82 (d, 4H, J = 6.9 Hz, PhH), 7.35 (d, 4H, J = 8.4 Hz, PhH); ESIMS (*m*/*z*): 430 $(M-HCl+H)^+$; HRMS (ESI): Calcd for $C_{24}H_{32}ClNO_4S$ – H: 464.1654310, found: 464.1656833.
Compound **5′d**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.58–1.72 (m, 2H), 2.17 (s, 3H, —CH_3Ph), 2.27–2.35 (m, 1H), 2.37 (s, 3H, —CH_3Ph), 2.52 (s, 3H, —CH_3Ph), 2.69–2.80 (m, 2H), 2.87–3.07 (m, 3H), 3.23–3.35 (m, 1H), 3.54–3.60 (m, 1H), 3.74–3.83 (m, 1H), 5.89 (s, 1H, —CHS—),7.07–7.16 (m, 4H, PhH), 7.25–7.28 (m, 1H, PhH), 7.71–7.73 (m, 1H, PhH), 7.76–7.77 (m, 1H, PhH); ESIMS (*m*/*z*): 446 $(M-H)^-$, 410 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{25}H_{34}ClNO_2S$ – H: 446.1923390, found: 446.1926013.

23. *Data for compounds* **6a**–**d**.
Compound **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ: 1.13–1.49 (m, 2H), 1.51–1.64 (m, 3H), 1.96–2.50 (m, 2H), 2.51–2.63 (m, 2H), 2.64–2.72 (m, 2H), 2.77–2.95 (m, 2H), 5.42 (s, 0.5H, —CHS=O), 5.46 (m, 0.5H, —CHS=O), 7.20–7.28 (m, 1H), 7.32–7.39 (m, 6H), 7.68–7.81 (m, 3H); ESIMS (*m*/*z*): 370 $(M-HCl-H)^-$; HRMS (ESI): Calcd for $C_{21}H_{26}ClNO_3S$ – H: 406.1236840, found: 406.1238185.
Compound **6b**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.18–1.38 (m, 3H), 1.52–1.73 (m, 2H), 1.96–2.08 (m, 2H), 2.19 (s, 6H, —CH_3), 2.53–2.91 (m, 4H), 3.00–3.27 (m, 2H), 5.35 (s, 0.5H, —CHS=O), 5.39 (s, 0.5H, —CHS=O), 7.10–7.41 (m, 6H), 7.57–7.75 (m, 2H); ESIMS (*m*/*z*): 434 $(M-H)^-$, 398 $(M-HCl)^-$; HRMS (ESI): Calcd for $C_{23}H_{30}ClNO_3S$ – H: 434.1563770, found: 434.1562158.
Compound **6c**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.20–1.36 (m, 2H),1.68–1.84 (m, 2H), 1.97–2.35 (m, 1H), 2.57–2.73 (m, 1H), 2.88–3.08 (m, 6H), 3.38–3.49 (m, 1H), 3.60 (s, 6H, —OCH_3), 5.41 (s, 1H, —CHS=O), 6.81–7.14 (m, 4H), 7.37–7.72 (m, 4H); ESIMS (*m*/*z*): 435 $(M-H)^-$; HRMS (ESI): Calcd for $C_{23}H_{30}ClNO_3S$ – H: 435.16349, found: 435.16361.
Compound **6d**: ^{1}H NMR (300 MHz, C_5D_5N): δ: 1.57–1.64 (m, 3H), 1.86–1.92 (m, 1H), 2.02–2.13 (m, 1H), 2.17 (s, 3H), 2.24–2.27 (m, 1H), 2.31–2.36 (m, 3H), 2.41–2.57 (m, 3H), 2.60–2.84 (m, 6H), 3.05–3.23 (m, 1H), 5.88–5.97 (m, 1H, —CHS=O), 7.08–7.32 (m, 5H), 7.57–7.92 (m, 2H); ESIMS (*m*/*z*): 448 $(M-H)^-$; HRMS (ESI): Calcd for $C_{24}H_{32}ClNO_3S$ – H: 448.17141, found: 448.17187.