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ORIGINAL PAPER

Synthesis and biological evaluation of benzothiazol-based 1,3,4-oxadiazole derivatives as amyloid β-targeted compounds against Alzheimer's disease

Wen-wen Mei[1,3] · Sha-sha Ji[2,3] · Wei Xiao[6] · Xue-dong Wang[3] · Cheng-shi Jiang[1,4] · Wen-quan Ma[5] · Hai-yan Zhang[2] · Jing-xu Gong[1] · Yue-wei Guo[1]

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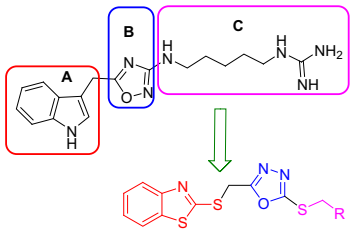
Abstract A series of new benzothiazol-based 1,3,4-oxadiazole derivatives were synthesized and evaluated for their neuroprotective effects against $A\beta_{25-35}$-induced toxicity in SH-SY5Y cells. The bioassay results indicated that most of the tested compounds exhibited promising neuroprotective activity. In particular, compound 2-[[[5-[(4-bromophenylmethyl)thio]-1,3,4-oxadiazol-2-yl]methyl]thio]-benzothiazole showed the most potent activity (95.7% of cell viability at 10 μM), better than the positive control EGCG (90.7% of cell viability at 10 μM). Furthermore, compounds 2-[[[5-[(2-bromophenylmethyl)thio]-1,3,4-oxadiazol-2-yl]methyl]thio]benzothiazole, 2-[[[5-[(4-bromo-2-fluorophenylmethylyl)thio]-1,3,4-oxadiazol-2-yl]methyl]-thio]benzothiazole, and 2-[[[5-[(4-methoxyphenyl-methyl)thio]-1,3,4-oxadiazol-2-yl]methyl]thio]benzothiazole displayed neuroprotective activity similar to EGCG (87.7, 89.1, and 87.7% of cell viability, respectively, at 10 μM). The preliminary SARs analysis indicated that benzene ring is the key factor for the neuroprotective activity and the bromo atom substituted at 4-position of the benzene ring favors the neuroprotective activity. In addition, the fluoro group in the benzene ring appears not beneficial for the neuroprotective activity.

Graphical abstract



Keywords Structure–activity relationships · Heterocycles · Drug research · Neuroprotective effects

Wen-wen Mei, Sha-sha Ji, and Wei Xiao contributed equally to this work.

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✉ Hai-yan Zhang
hzhang@simm.ac.cn

✉ Jing-xu Gong
jxgong@mail.shcnc.ac.cn

1 State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zi Road, Zhangjiang Hi-Tech Park, Shanghai 201203, People's Republic of China

2 CAS Key Laboratory of Receptor Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, People's Republic of China

3 College of Pharmacy, Weifang Medical University, Shandong, People's Republic of China

4 School of Biological Science and Technology, University of Jinan, Shandong, People's Republic of China

5 Weifang Biomedical Innovation and Entrepreneurship Service Center, Shandong, People's Republic of China

6 Jiangsu Kanion Pharmaceutical Co. Ltd, Lianyungang, Jiangsu, People's Republic of China

Introduction

Alzheimer's disease (AD), known as the most prevalent type of dementia, is a progressive neurodegenerative disease which causes symptoms of memory loss and cognitive

impairment, eventually lead to the loss of cognitive function [1]. AD, which affected 36 million people worldwide in recent years, has placed a heavy burden on family and decreased the quality of life in patients, but even worse, the numbers of AD patients are estimated to increase up to 114 million by 2050 [2]. Therefore, scientific researchers have put massive efforts to better understanding of the pathogenesis of the disease as well as developing effective therapeutic agents to be able to prevent or to cure AD [3–6]. However, to date, no satisfactory treatment has been proved to prevent or cure AD. For this reason, there is an urgent need for developing new drugs being able to limiting and stopping the process of AD.

Although AD pathogenesis is multifaceted and difficult to pinpoint, genetic and pathological evidence strongly supports that amyloid-beta (Aβ) plays an early and vital - role in AD [7]. An alternative hypothesis indicates that Aβ can cause cellular toxicity, which ultimately results in neuronal dysfunction and death. Therefore, development of active compounds to improve Aβ-associated neurotoxicity has been taken up as a promising therapeutic strategy against AD [8].

Marine nature products (MNPs) have drawn the attention of both medicinal chemists and pharmacologists for several decades, due to their chemical diversities and various biological activities as well. MNPs have played and continued playing a vital role in the development of new drugs and drug candidates [9–12]. Marine alkaloids exhibit various kinds of pharmacological activities such as antitrypanosomal, antibacterial, antimalarial, anti-infective activities, and so on [13, 14]. Our group has long engaged in isolation, synthesis, and biological evaluation of MNPs from the South China Sea marine organisms for many years, and in the course of these efforts, recently, two novel alkaloids, phidianidines A (**1a**) and B (**1b**) (Fig. 1), have been isolated from the opisthobranch mollusk *Phidiana militaris*. These two alkaloids, featured by the first identified MNPs bearing an uncommon 1,2,4-oxadiazole moiety, exhibited promising antitumor activity against C6 and HeLa cells with IC_{50} values of 0.64 and 0.14 μM, respectively [15]. Phidianidines have attracted many researchers' interests due to their unique structure and excellent bioactivity [16, 17]. In addition, phidianidine A was found to be a novel potential ligand

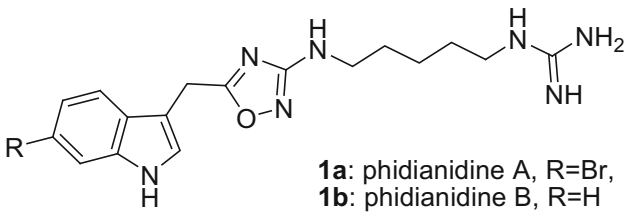


Fig. 1 Structures of phidianidines A and B

of CXCR4, a chemokine receptor deeply involved in HIV infection, rheumatoid arthritis, cancer development/progression, and metastasization [18]. Interestingly, phidianidines were found to be selective inhibitors of dopamine transporter (DAT) as well as partial agonist of the μ opioid receptor, these results enlightening us that they can be utilized for developing new ligands or ligand analogs for central nervous system (CNS) targets. Recently, a series of phidianidine-based derivatives have been synthesized and some derivatives exhibited promising neuroprotective effects against amyloid-beta 25–35 ($Aβ_{25–35}$)-, hydrogen peroxide (H_2O_2)-, or oxygen-glucose deprivation (OGD)-induced neurotoxicity in SH-SY5Y cells [19]. These results provoked our great interest in further exploring neuroprotective activities of phidianidine-based compounds. In this communication, the neuroprotective effects against $Aβ_{25–35}$-induced toxicity in SH-SY5Y cells of new benzothiazol-based 1,3,4-oxadiazole derivatives are reported.

Results and discussion

Chemistry

Analysis of the structural characteristic of phidianidines A and B, as shown in Fig. 2, reveals that their structures contained three partials, namely moiety A, B, and C. The moiety A, the indole motif is an important pharmacophore widely presented in numerous bioactive natural products or drugs [20]. The moiety B, the 1,2,4-oxadiazole ring has been incorporated in drug discovery programs as an essential element of pharmacophore in contribution of ligand binding [21, 22]. Our previous preliminary structure–activity relationships (SAR) study about the moiety C suggested that the guanidine structure was not required for neuroprotective activity [19], while the different substituted benzene rings which replaced the guanidine moiety play a crucial role for their bioactivity.

Benzothiazole (BTA) scaffold, the main moiety of traditional amyloid-binding dyes-thioflavin-T (ThT) [23], exhibited strong affinity for amyloid fibrils and was used as promising imaging agents targeting to Aβ plaques [24–26]. In addition, compounds contain BTA moiety are quite capable of inhibiting Aβ aggregation [27–29] as well as Aβ induced neurotoxicity [30, 31]. In another hand, oxadiazoles are a class of heterocyclic compounds with broad spectrum of biological activities [32–36], specially the 1,3,4-oxadiazole derivatives displayed excellent affinity for Aβ aggregates [37] including excellent affinity for Aβ aggregates [38, 39]. All this evidences suggest that combining 1,3,4-oxadiazole fragment with BTA moiety might be a potential therapeutic strategy for AD. In this work,

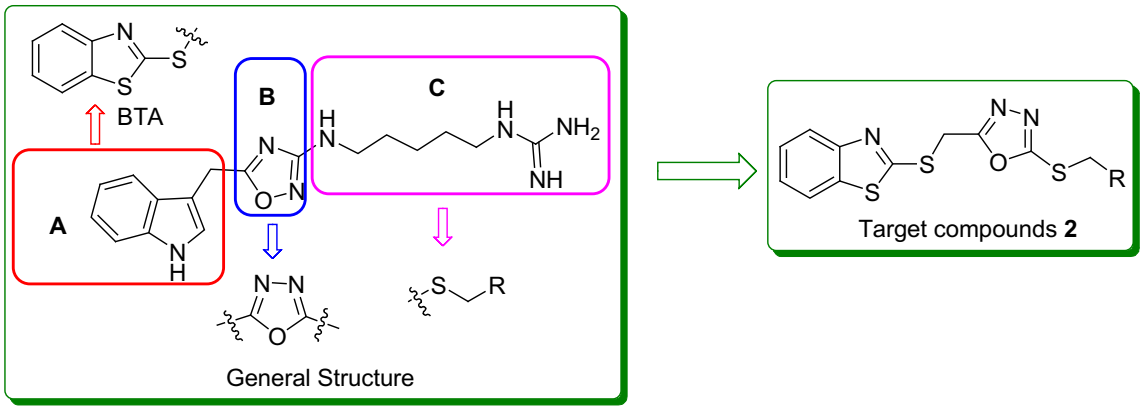


Fig. 2 Structural modifications

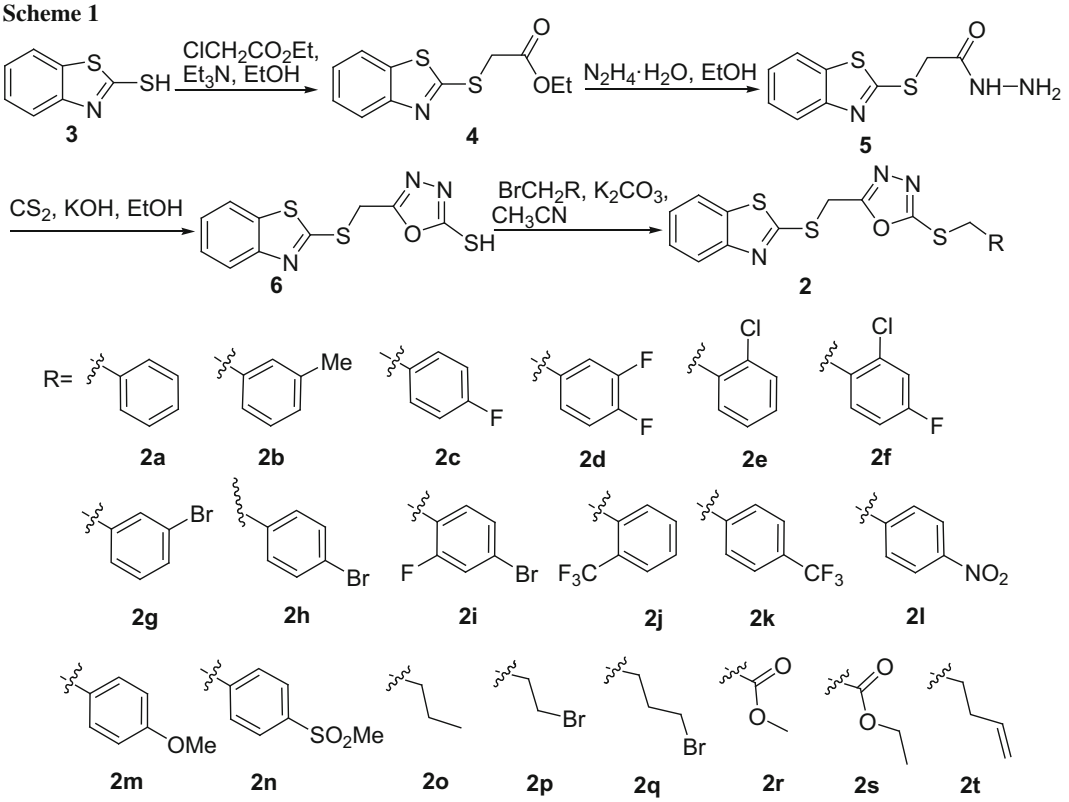
1,3,4-oxadiazole was introduced to moiety B to replace 1,2,4-oxadiazole. Substituted benzylthio group or different alkylthio groups were reserved as moiety C. Accordingly, we designed a series of novel phidianidines analogs **2** bearing different terminal groups (Fig. 2).

The synthetic route of compounds **2** is shown in Scheme 1. First, commercially available 1,3-benzothiazole-2-thiol (**3**) was reacted with ethyl chloroacetate to produce ester **4** in 95% yield [40]. Then, treatment of the ester **4** with 80% hydrazine hydrate in refluxing EtOH gave hydrazide **5** in 80% yield [41]. Furthermore, the key intermediate **6** was formed via reactions of hydrazide **5** with carbon disulfide in the presence of KOH under refluxing EtOH in 70% yield [41]. Finally, the intermediate **6** was converted into **2** in good yield by reacting with different substituted benzyl bromide in the presence of K_2CO_3 using CH_3CN as solvent.

Pharmacology

The influence of the compounds on cell viabilities of SH-SY5Y with or without $A\beta_{25–35}$ exposure was measured.

Scheme 1



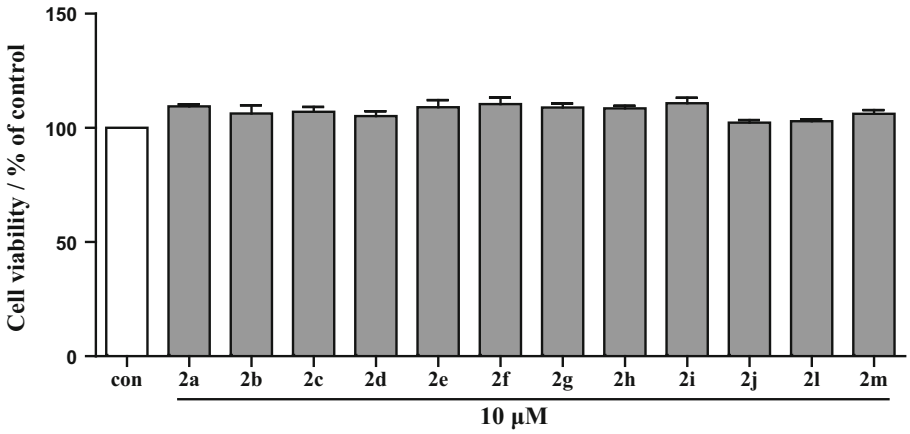


Fig. 3 Effects of compounds alone on cell viability of SH-SY5Y cells without $A\beta_{25-35}$ exposure. The cell viability was expressed as percentage of the untreated control (100%). Values are mean ± SEM of at least three independent experiments

The active neuroprotective compounds (10 μM) did not cause notable changes in cell viability of SH-SY5Y cells, when incubating with the cells for 24 h (Fig. 3). These compounds exhibited significant neuroprotective effects against $A\beta_{25-35}$-induced neurotoxicity in SH-SY5Y cells, and the screening data are shown in Table 1. SH-SY5Y cells exposed to 10 μM $A\beta_{25-35}$ for 24 h resulted in decrease cell viability (63.2%) as compared with control. As listed in the table, compounds **2a–2m** (except for **2k**) markedly attenuated $A\beta_{25-35}$-induced cytotoxicity at the concentration of 10 μM with cell viabilities ranged from 74.6 to 95.7%, while compounds **2n–2t** showed no activity. All the test compounds at 1 μM did not show beneficial effects against $A\beta_{25-35}$-induced neurotoxicity. As a positive control, EGCG showed 72.3 and 90.7% of cell viability at 1 and 10 μM, respectively. Compound **2h** bearing bromo group at the 4-position of the benzene ring showed the strongest activity (95.7% of cell viability at 10 μM), better than the positive control EGCG. In addition, the neuroprotective effects of 2-chlorine compound **2e** (87.7% of cell viability at 10 μM), 2-fluoro-4-bromo compound **2i** (89.1% of cell viability at 10 μM), and 4-methoxy compound **2m** (87.7% of cell viability at 10 μM) were comparable with EGCG. Furthermore, a significant change in cell viability of SH-SY5Y cells was not observed when the cells were incubated with 10 μM of active compounds for 24 h in $A\beta_{25-35}$-free condition (Fig. 3). This result indicates that the neuroprotective activity of compounds may not be attributed to the promotion of cell proliferation.

Table 1 Protective effects of compounds against $A\beta_{25-35}$-induced neurotoxicity in SH-SY5Y cells

Compound	Cell viability/% (10 μM)	Compound	Cell viability/% (10 μM)
2a	79.8	**2k**	–
2b	79.6	**2l**	85.0
2c	74.6	**2m**	87.7
2d	77.9	**2n**	–
2e	87.7	**2o**	–
2f	80.3	**2p**	–
2g	84.4	**2q**	–
2h	95.7	**2r**	–
2i	89.1	**2s**	–
2j	78.2	**2t**	–
		EGCG	90.7

The cell viability was expressed as percentage of the untreated control (100%). Values are means of three independent experiments. The cell viability under $A\beta_{25-35}$ exposure was 63.2 ± 1.3%. EGCG was employed as positive control

"–", no protection

A primary structure–activity relationship (SAR) study showed that the R group in moiety C is essentially important for the bioactivity. In fact, most synthesized compounds bearing benzene rings as R groups exhibited potent neuroprotective activity against $A\beta_{25-35}$-induced neurotoxicity, while compounds with R group bearing alkyl or ester showed no activity. Compared with compound **2a**, the introduction of fluoro groups in the benzene ring (**2c**, **2d**) decreased the neuroprotective activity. Coincidentally, the unanimous conclusion was reached from the comparison of 2-chloro compound **2e** and 2-chloro-4-fluoro compound **2f** as well as the comparison of 4-bromo compound **2h** and 2-fluoro-4-bromo compound **2i**. Interestingly, trifluoromethyl substitution at C-4 position in the benzene ring (**2k**) led to the loss of neuroprotective activity, while 2-trifluoromethyl compound **2j** exhibited neuroprotective activity (78.2% of cell viability at 10 μM), indicating that the CF_3 group at C-2 position might be helpful for the neuroprotective activity. However, the opposite result has been observed for the 4-bromo substituted compound **2h**, which showed the highest activity (95.7% of cell viability at 10 μM) among all the tested compounds. Such result suggested that the activity of the compounds should not only be influenced by

the position of the substituted group (e.g., 4-CF_3 vs. 2-CF_3), but also by the group itself (e.g., 4-CF_3 vs. 4-Br). Compound **2n**, bearing a bulky sulfoxide group at 4-position in the benzene ring, was lack of neuroprotective activity probably due to the strong steric hindrance. In addition, the replacement of electron-withdrawing groups (trifluoromethyl, sulfoxide, or halogen groups) with electron-releasing groups (such as methoxyl group) provided the corresponding **2m**, which still showed potent neuroprotective activity (87.7% of cell viability at 10 μM), indicating that electronic effect of the substitution in 4-position might not be a key factor in their neuroprotective activity against $A\beta_{25-35}$-induced neurotoxicity.

Conclusion

In the present work, a series of novel benzothiazol-based 1,3,4-oxadiazole derivatives were designed and synthesized, and their neuroprotective effects against $A\beta_{25-35}$-induced neurotoxicity in SH-SY5Y cells were evaluated. Based on the preliminary SAR analysis, most of the target compounds containing benzothiazol-based 1,3,4-oxadiazole skeleton showed potential neuroprotective activities. In particular, compound **2h** exhibited the neuroprotective activity superior to the positive control EGCG. While the neuroprotective activity of compound **2e**, **2i**, and **2m** was comparable with EGCG. The preliminary SAR study indicated that benzene ring played a pivotal role in neuroprotective activity and the position of substitution was important for activity. Bromo substitution at 4-position improved the neuroprotective activity. In addition, groups contain fluoro on the benzene ring which was not conducive to the activity. The pharmacological data obtained here may be useful for the design of novel neuroprotective compounds with the skeleton of benzothiazol-based 1,3,4-oxadiazole derivatives. Further studies to improve the neuroprotective effect and in vivo bioassay of this class of compounds are in progress.

Experimental

The starting materials and reagents, purchased from commercial suppliers, were used without further purification. All solvents used for the reactions were dried prior to use according to standard procedures. All primary reagents were commercially available. Anal. TLC: precoated G60 F-254 silica gel plates (SiO_2; Yan Tai Zi Fu Chemical Group Co.). Column chromatography (CC): silica gel (SiO_2, 200–300 mesh; Qing Dao Hai Yang Chemical Group Co.), solvents were of analytical grade. NMR spectra: Bruker Avance spectrometer (400 MHz for ^1H and 100 or 150 MHz for ^{13}C), using the residual $CHCl_3$ signal ($\delta(H) = 7.26$ ppm) as an internal standard for ^1H NMR and $CDCl_3$ signal ($\delta(C) = 77.0$ ppm) for ^{13}C NMR; δ in ppm, J in Hz. ESI–MS: Q-TOF Micro LC/MS–MS mass spectrometer. EI-MS: Finnigan-MAT-95 mass spectrometer.

Methyl 2-(benzo[d]thiazol-2-ylthio)acetate (**4**)
To a solution of 3.34 g 1,3-benzothiazol-2-ylthiol **3** (20.00 mmol), triethylamine (25.00 mmol) in EtOH was added 5 cm^3 ethyl chloroacetate (25.00 mmol). The reaction mixture was refluxed in 20 cm^3 EtOH for 3 h. After removal of EtOH under reduced pressure, the resulting mixture was recrystallized with EtOH to obtain white crystals (3.80 g, 75.10%). The spectra of acetate **4** were similar to the Ref. [39].

2-(Benzo[d]thiazol-2-ylthio)acetohydrazide (**5**)
Compound **4** (3.80 g, 15.02 mmol) and 2.4 cm^3 80% hydrazine hydrate (40.00 mmol) in 30 cm^3 EtOH were refluxed for 14 h. After removal of solvent under reduced pressure, the resulting mixture was recrystallized with EtOH to obtain white crystals (3.30 g, 84.83%). The spectra of hydrazide **5** were similar to Ref. [41].

5-[(Benzo[d]thiazol-2-ylthio)methyl]-1,3,4-oxadiazole-2-thiol (**6**)
A mixture of 3.30 g hydrazide **5** (12.74 mmol), 1.70 g KOH (30.00 mmol), and 2 cm^3 CS_2 (30 mmol) was refluxed in 20 cm^3 EtOH for 18 h. After completion of the reaction, the reaction solution was concentrated under reduced pressure, and 30 cm^3 ethyl acetate was added and neutralized to slight acidity (pH ~6) by HCl. Then, the resulting mixture was extracted with ethyl acetate and purified by silica-gel chromatography (EtOAc/hexanes, 1:4) to yield the product as an pale yellow powder (2.6 g, 72.87%). The spectra of thiol **7** were similar to the Ref. [42].

General procedure for preparation of compounds 2

A mixture of 84 mg thiol **6** (0.30 mmol), 0.42 g K_2CO_3 (3.00 mmol), and bromide (0.60 mmol) was stirred for 4 h in CH_3CN at room temperature. The reaction solution was concentrated under reduced pressure, and was extracted with CH_2Cl_2. The organic layer was concentrated and was purified by silica gel column chromatography to afford benzothiazol-based 1,3,4-oxadiazole derivatives **2a–2t**, respectively.

2-[[5-(Phenylmethylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2a**, $C_{17}H_{13}N_3OS_3$)
Yield 44.0%; white solid; m.p.: 96–100 °C; $R_f = 0.44$ (petroleum ether:acetone 3:1); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.96–7.89$ (m, 1H, Ar–H), 7.80 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.52–7.43 (m, 1H, Ar–H), 7.43–7.25 (m, 6H, Ar–H), 4.82 (s, 2H, $–CH_2–$), 4.44 (s, 2H,

–CH_2–) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.1 (C), 164.0 (C), 163.2 (C), 152.7 (C), 135.7 (C), 135.3 (C), 129.1 (CH), 128.8 (CH), 128.1(CH), 126.3 (CH), 124.8 (CH), 122.0 (CH), 121.2 (CH), 36.7(CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{13}N_3OS_3$ (M^+) 371.0221, found 371.0220.

2-[[5-[(3-Methylphenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2b**, $C_{18}H_{15}N_3OS_3$)
Yield 83.1%; yellow solid; m.p.: 58–68 °C; R_f = 0.42 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95–7.90 (m, 1H, Ar–H), 7.80–7.76 (m, 1H, Ar–H), 7.50–7.42 (m, 1H, Ar–H), 7.38–7.30 (m, 1H, Ar–H), 7.24–7.14 (m, 3H, Ar–H), 7.13–7.07 (m, 1H, Ar–H), 4.81 (s, 2H, –CH_2–), 4.40 (s, 2H, –CH_2–), 2.34 (s, 3H, –CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2 (C), 163.9 (C), 163.2 (C), 152.7 (C), 138.6 (C), 135.6 (C), 135.2 (C), 129.8 (CH), 128.9 (CH), 128.7 (CH), 126.3 (CH), 126.2 (CH), 124.8 (CH), 122.0 (CH), 121.2 (CH), 36.75 (CH_2), 26.2 (CH_2), 21.4 (CH_3) ppm; HREI-TOF: *m/z* calcd. for $C_{18}H_{15}N_3OS_3$ (M^+) 385.0377, found 385.0370.

2-[[5-[(3-Fluorophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2c**, $C_{17}H_{12}FN_3OS_3$)
Yield 94.3%; yellow solid; m.p.: 91–96 °C; R_f = 0.38 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.80 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.51–7.43 (m, 1H, Ar–H), 7.41–7.32 (m, 3H, Ar–H), 7.04–6.95 (m, 2H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.40 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.9 (C), 164.1 (C), 163.1 (C), 162.5 (d, *J* = 246.0 Hz, C), 152.7 (C), 135.7 (C), 131.3 (d, *J* = 3.3 Hz, C), 130.9 (d, *J* = 8.3 Hz, CH), 126.3 (CH), 124.8 (CH), 122.0 (CH), 121.21 (CH), 115.7 (d, *J* = 21.0 Hz, CH), 35.9 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{12}FN_3OS_3$ (M^+) 389.0127, found 389.0125.

2-[[5-[(3,4-Difluorophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2d**, $C_{17}H_{11}F_2N_3OS_3$)
Yield 57.3%; white solid; m.p.: 85–92 °C; R_f = 0.36 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 1H, Ar–H), 7.80 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.51–7.43 (m, 1H, Ar–H), 7.40–7.33 (m, 1H, Ar–H), 7.28–7.21 (m, 1H, Ar–H), 7.16–7.01 (m, 2H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.37 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.5 (C), 164.2 (C), 163.1 (C), 152.7 (C), 151.0 (t, *J* = 13.0 Hz, C), 149.3 (t, *J* = 13.0 Hz, C), 135.7 (C), 132.6 (t, *J* = 4.5 Hz, C), 126.3 (CH), 125.3 (dd, *J* = 6.4, 3.7 Hz, CH), 124.9 (CH), 122.0 (CH), 121.2 (CH), 118.2 (d, *J* = 17.9 Hz, CH), 117.5 (d, *J* = 17.5 Hz, CH), 35.6 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{11}F_2N_3OS_3$ (M^+) 407.0032, found 407.0028.

2-[[5-[(2-Chlorophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2e**, $C_{17}H_{12}ClN_3OS_3$)
Yield 64.2%; white solid; m.p.: 66–75 °C; R_f = 0.34 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.75 (d, *J* = 7.6 Hz, 1H, Ar–H), 7.51 (dd, *J* = 7.5, 1.7 Hz, 1H, Ar–H), 7.46–7.39 (m, 1H, Ar–H), 7.38–7.27 (m, 2H, Ar–H), 7.20 (td, *J* = 7.7, 1.8 Hz, 1H, Ar–H), 7.14 (td, *J* = 7.5, 1.3 Hz, 1H, Ar–H), 4.79 (s, 2H, –CH_2–), 4.51 (s, 2H, –CH_2–) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.0 (C), 164.1 (C), 163.2 (C), 152.6 (C), 135.6 (C), 134.27 (C), 133.5 (C), 131.4 (CH), 129.7 (CH), 129.6 (CH), 127.0 (CH), 126.3 (CH), 124.8 (CH), 121.9 (CH), 121.2 (CH), 34.5 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{12}ClN_3OS_3$ (M^+) 404.9831, found 404.9815.

2-[[5-[(2-Chloro-4-fluorophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2f**, $C_{17}H_{11}ClFN_3OS_3$)
Yield 92.4%; yellow solid; m.p.: 66–71 °C; R_f = 0.43 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1, 1H, Ar–H), 7.79 (d, *J* = 8.0, 1H, Ar–H), 7.55 (dd, *J* = 8.6, 6.0 Hz, 1H, Ar–H), 7.48–7.42 (m, 1H, Ar–H), 7.35 (td, *J* = 7.7, 1.2 Hz, 1H, Ar–H), 7.14 (dd, *J* = 8.4, 2.6 Hz, 1H, Ar–H), 6.90 (td, *J* = 8.3, 2.6 Hz, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.50 (s, 2H, –CH_2–) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 164.5 (C), 163.8 (C), 162.7 (C), 161.8 (d, *J* = 249.5 Hz, C), 152.2 (C), 135.2 (C), 134.7 (d, *J* = 10.4 Hz, C), 132.1 (d, *J* = 8.9 Hz, C), 129.2 (d, *J* = 3.5 Hz, CH), 125.9 (CH), 124.4 (CH), 121.5 (CH), 120.8 (CH), 116.8 (d, *J* = 25.0 Hz, CH), 113.8 (d, *J* = 21.0 Hz, CH), 33.4 (CH_2), 25.7 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{11}ClFN_3OS_3$ (M^+) 422.9737, found 422.9717.

2-[[5-[(3-Bromophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2g**, $C_{17}H_{12}BrN_3OS_3$)
Yield 61.5%; yellow oil; R_f = 0.35 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H, Ar–H), 7.56 (s, 1H, Ar–H), 7.51–7.38 (m, 2H), Ar–H, 7.38–7.30 (m, 2H, ArH, Ar–H), 7.16 (t, *J* = 7.8 Hz, 1H, Ar–H), 4.81 (s, 2H, –CH_2–), 4.37 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.6 (C), 164.2 (C), 163.1 (C), 152.7 (C), 137.8 (C), 135.7 (C), 132.0 (CH), 131.2 (CH), 130.3 (CH), 127.8 (CH), 126.3 (CH), 124.8 (CH), 122.7 (C), 122.0 (CH), 121.2 (CH), 35.9 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{12}BrN_3OS_3$ (M^+) 448.9326, found 448.9317.

2-[[5-[(4-Bromophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2h**, $C_{17}H_{12}BrN_3OS_3$)
Yield 85%; white solid, m.p.: 96–100 °C; R_f = 0.35 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.94–7.88 (m, 1H, Ar–H), 7.79 (dd, J = 8.0, 0.6 Hz, 1H, Ar–H), 7.50–7.39 (m, 3H, Ar–H), 7.38–7.33 (m, 1H, Ar–H), 7.30–7.23 (m, 2H, Ar–H), 4.81 (s, 2H, –CH_2), 4.36 (s, 2H, –CH_2) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.7 (C), 164.1 (C), 163.1 (C), 152.7 (C), 135.6 (C), 134.6 (C), 131.0 (CH), 130.8 (CH), 126.4 (CH), 124.9 (CH), 122.2 (C), 122.0 (CH), 121.2 (CH), 36.0 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{12}BrN_3OS_3$ (M^+) 448.9326, found 448.9331.

2-[[5-[(4-Bromo-3-fluorophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2i**, $C_{17}H_{11}BrFN_3OS_3$)
Yield 78.3%; yellow solid; m.p.: 82–85 °C; R_f = 0.40 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.1 Hz, 1H, Ar–H), 7.78 (d, J = 8.0 Hz, 1H, Ar–H), 7.50–7.42 (m, 1H, Ar–H), 7.39–7.31 (m, 2H, Ar–H), 7.25–7.15 (m, 2H, Ar–H), 4.80 (s, 2H, –CH_2–), 4.38 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.6 (C), 164.3 (C), 163.1 (C), 160.6 (d, J = 252.0 Hz, C), 152.7 (C), 135.6 (C), 132.3 (d, J = 3.8 Hz, CH), 127.6 (d, J = 3.7 Hz, CH), 126.3 (CH), 124.84 (CH), 122.6 (d, J = 9.5 Hz) (C), 122.4 (d, J = 15.0 Hz, C), 122.0(CH), 121.2 (CH), 119.3 (d, J = 64.0 Hz, CH), 29.5 (d, J = 2.8 Hz, CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{11}BrFN_3OS_3$ (M^+) 466.9232, found 466.9221.

2-[[5-[[2-(Trifluoromethyl)phenyl]methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2j**, $C_{18}H_{12}F_3N_3OS_3$)
Yield 83.5%; white solid; m.p.: 95–98 °C; R_f = 0.30 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz): δ = 7.91 (d, J = 8.1 Hz, 1H, Ar–H), 7.79 (d, J = 7.9 Hz, 1H, Ar–H), 7.69 (dd, J = 18.9, 7.6 Hz, 2H, Ar–H), 7.52-7.31 (m, 4H, Ar–H), 4.83 (s, 2H, –CH_2–), 4.64 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz): δ = 165.1 (C), 164.3 (C), 163.1 (C), 152.7 (C), 135.6 (C), 134.3 (C), 132.4 (CH), 132.0 (CH), 128.7 (q, J = 30.0 Hz, C), 128.4 (CH), 126.4 (q, J = 5.5 Hz, CH), 126.3 (CH), 124.8 (CH), 124.2 (d, J = 273.0 Hz, CF_3), 122.0 (CH), 121.2 (CH), 33.2 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{18}H_{12}F_3N_3OS_3$ (M^+) 439.0095, found 439.0096.

2-[[5-[[4-(Trifluoromethyl)phenyl]methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2k**, $C_{18}H_{12}F_3N_3OS_3$)
Yield 83.5%; yellow solid; m.p.: 90–96 °C; R_f = 0.31 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.91 (d, J = 8.1 Hz, 1H, Ar–H), 7.80 (d, J = 8.0 Hz, 1H, Ar–H), 7.54 (q, J = 8.4 Hz, 4H, Ar–H), 7.47 (t, J = 7.7 Hz, 1H, Ar–H), 7.36 (t, J = 7.6 Hz, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.46 (s, 2H, –CH_2–) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.5 (C), 164.3 (C), 163.1 (C), 152.7 (C), 139.7 (C), 135.6 (C), 130.3 (q, J = 33.0 Hz, C), 129.4 (CH), 126.3 (CH), 125.7 (q, J = 33.0 Hz, CH), 124.9 (CH), 123.9 (d, J = 270.0 Hz, CF_3), 122.0 (CH), 121.2 (CH), 35.9 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{18}H_{12}F_3N_3OS_3$ (M^+) 439.0095, found 439.0096.

2-[[5-[(4-Nitrophenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2l**, $C_{17}H_{12}N_4O_3S_3$)
Yield 71.3%; white solid; m.p.: 98–102 °C; R_f = 0.20 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.88 (m, 1H), 7.82–7.76 (m, 1H, Ar–H), 7.51–7.38 (m, 3H, Ar–H), 7.38–7.33 (m, 1H, Ar–H), 7.30–7.24 (m, 2H, Ar–H), 4.81 (s, 2H, –CH_2–), 4.36 (s, 2H, –CH_2–) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 164.5 (C), 164.1 (C), 163.0 (C), 152.6 (C), 147.5 (C), 143.2 (C), 135.6 (C), 130.0 (CH), 126.4 (CH), 124.9 (CH), 123.9 (CH), 121.9 (CH), 121.35 (CH), 35.5 (CH_2), 26.1 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{17}H_{12}N_4O_3S_3$ (M^+) 416.0072, found 416.0068.

2-[[5-[(4-Methoxyphenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2m**, $C_{18}H_{15}N_3O_2S_3$)
Yield 63.2%; yellow solid; m.p.: 58–67 °C; R_f = 0.34 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.92 (dd, J = 8.2, 0.5 Hz, 1H, Ar–H), 7.79 (dd, J = 8.0, 0.6 Hz, 1H, Ar–H), 7.51–7.42 (m, 1H, Ar–H), 7.39–7.25 (m, 3H, Ar–H), 6.87–6.79 (m, 2H, Ar–H), 4.81 (s, 2H, –CH_2–), 4.39 (s, 2H, –CH_2–), 3.79 (s, 3H, –CH_3) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.2 (C), 163.8 (C), 163.2 (C), 159.4 (C), 152.7 (C), 135.6 (C), 130.3 (CH), 127.2 (C), 126.3 (CH), 124.8 (CH), 121.9 (CH), 121.2 (CH), 114.1 (CH), 55.3 (CH_3), 36.4 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{18}H_{15}N_3O_2S_3$ (M^+) 401.0326, found 401.0318.

2-[[5-[(4-Methylsulfonylphenyl)methylthio]-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2n**, $C_{18}H_{15}N_3O_3S_4$)
Yield 89.0%; white solid; m.p.: 120–123 °C; R_f = 0.44 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94–7.83 (m, 3H, Ar–H), 7.82–7.75 (m, 1H, Ar–H), 7.60 (d, J = 8.4 Hz, 2H, Ar–H), 7.49–7.41 (m, 1H, Ar–H), 7.38–7.31 (m, 1H, Ar–H), 4.80 (s, 2H, –CH_2–), 4.45 (s, 2H, –CH_2–), 3.02 (s, 3H, –CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): δ = 164.4 (C), 164.2 (C), 163.1 (C), 152.7 (C), 142.2 (C), 140.1 (C), 135.6 (C), 130.1 (CH), 127.8 (CH), 126.4 (CH), 124.9 (CH), 121.9 (CH), 121.3 (CH), 44.5 (CH_3), 35.7 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{18}H_{15}N_3O_3S_4$ (M^+) 448.9996, found 448.9993.

2-[[5-(Butylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2o**, $C_{14}H_{15}N_3OS_3$)
Yield 78.1%; yellow solid; m.p.: 45–52 °C; R_f = 0.42 (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, J = 8.1 Hz, 1H, Ar–H), 7.76 (d, J = 8.0 Hz, 1H, Ar–H), 7.48–7.39 (m, 1H, Ar–H),

7.35–7.25 (m, 1H, ArH), 4.80 (s, 2H, –CH_2–), 3.18 (t, $J = 8.0$ Hz, 2H, –CH_2–), 1.78–1.65 (m, 2H, –CH_2–), 1.47–1.34 (m, 2H, –CH_2–), 0.90 (t, $J = 7.4$ Hz, 3H, –CH_3) ppm; ^{13}C NMR (151 MHz, $CDCl_3$): $\delta = 165.8$ (C), 163.7 (C), 163.2 (C), 152.7 (C), 135.6 (C), 126.3 (CH), 124.8 (CH), 121.9 (CH), 121.2 (CH), 32.2 (CH_2), 31.2 (CH_2), 26.3 (CH_2), 21.7 (CH_2), 13.5 (CH_3) ppm; HREI-TOF: *m/z* calcd. for $C_{14}H_{15}N_3OS_3$ (M^+) 337.0377, found 337.0377.

2-[[5-(2-Bromopropylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2p**, $C_{13}H_{12}BrN_3OS_3$)
Yield 66.3%; yellow oil; $R_f = 0.30$ (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 8.0$ Hz, 1H, Ar–H), 7.79 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.46 (ddd, $J = 8.2$, 7.3, 1.2 Hz, 1H, Ar–H), 7.35 (ddd, $J = 8.4$, 7.3, 1.1 Hz, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 3.49 (t, $J = 6.2$ Hz, 2H, –CH_2–), 3.35 (t, $J = 6.9$ Hz, 2H, –CH_2–), 2.37–2.28 (m, 2H, –CH_2–) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 164.6$ (C), 163.6 (C), 162.7 (C), 152.2 (C), 135.2 (C), 125.9 (CH), 124.4 (CH), 121.5 (CH), 120.8, (CH), 31.1 (CH_2), 30.9 (CH_2), 30.2 (CH_2), 25.8 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{13}H_{12}BrN_3OS_3$ (M^+) 400.9326, found 400.9334.

2-[[5-(3-Bromobutylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2q**, $C_{14}H_{14}BrN_3OS_3$)
Yield 69.0%; yellow oil; $R_f = 0.31$ (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.95$–7.89 (m, 1H, Ar–H), 7.82-7.76 (m, 1H, Ar–H), 7.51–7.41 (m, 1H, Ar–H), 7.39–7.31 (m, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 3.39 (t, $J = 6.3$, 2H, –CH_2–), 3.22 (t, $J = 6.9$ Hz, 2H, –CH_2–), 2.06–1.86 (m, 4H, –CH_2CH_2–) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 164.9$ (C), 163.5 (C), 162.7 (C), 152.3 (C), 135.2 (C), 125.9 (CH), 124.4 (CH), 121.5 (CH), 120.8 (CH), 32.1 (CH_2), 31.1 (CH_2), 30.8 (CH_2), 27.4 (CH_2), 25.8 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{14}H_{14}BrN_3OS_3$ (M^+) 414.9482, found 414.9482.

2-[[5-(Methoxycarbonylmethylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2r**, $C_{13}H_{11}N_3OS_3$)
Yield 85.0%; yellow oil; $R_f = 0.19$ (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 8.1$ Hz, 1H, Ar–H), 7.78 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.49–7.41 (m, 1H, Ar–H), 7.38–7.31 (m, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.04 (s, 2H, –CH_2–), 3.76 (s, 3H, –CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 167.3$ (CO), 163.9 (C), 163.7 (C), 162.6 (C), 152.2 (C), 135.2 (C), 125.9 (CH), 124.4 (CH), 121.5 (CH), 120.8 (CH), 52.8 (CH_3), 33.6 (CH_2), 25.7 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{14}H_{14}BrN_3O_3S_3$ (M^+) 352.9963, found 352.9950.

2-[[5-(Ethoxycarbonylmethylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2s**, $C_{14}H_{13}N_3O_3S_3$)
Yield 81.7%; yellow oil; $R_f = 0.20$ (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 8.1$ Hz, 1H), 7.78 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.49–7.42 (m, 1H, Ar–H), 7.38–7.30 (m, 1H, Ar–H), 4.82 (s, 2H, –CH_2–), 4.22 (q, $J = 7.1$ Hz, 2H, –CH_2–), 4.03 (s, 2H, –CH_2–), 1.27 (t, $J = 7.1$ Hz, 3H, –CH_3) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = 166.8$ (CO), 163.8 (C), 163.8 (C), 162.6 (C), 152.2 (C), 135.2 (C), 125.9 (CH), 124.4 (CH), 121.5 (CH), 120.8 (CH), 62.0 (CH_2), 33.8 (CH_2), 25.7 (CH_2), 13.6 (CH_3) ppm; HREI-TOF: *m/z* calcd. for $C_{14}H_{13}N_3O_3S_3$ (M^+) 367.0119, found 367.0128.

2-[[5-(4-Pentenylthio)-1,3,4-oxadiazol-2-yl]methylthio]benzothiazole (**2t**, $C_{15}H_{15}N_3O_3S_3$)
Yield 80.2%; yellow oil; $R_f = 0.40$ (petroleum ether:acetone 3:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.96$–7.87 (m, 1H), 7.76 (d, $J = 8.0$ Hz, 1H, Ar–H), 7.49–7.40 (m, 1H, Ar–H), 7.37–7.29 (m, 1H, Ar–H), 5.82–5.66 (m, 1H, –CH=), 5.12–4.92 (m, 2H, –C=CH_2), 4.80 (s, 2H, –CH_2–), 3.18 (t, $J = 7.3$ Hz, 2H, –CH_2–), 2.15 (q, $J = 7.1$ Hz, 2H, –CH_2–), 1.85 (qui, $J = 7.3$ Hz, 2H, –CH_2–) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 165.6$ (C), 163.7 (C), 163.2 (C), 152.7 (C), 136.8 (CH), 135.6 (C), 126.3 (CH), 124.8 (CH), 121.9 (CH), 121.2 (CH), 115.9 (=CH_2), 32.3 (CH_2), 31.7 (CH_2), 28.2 (CH_2), 26.2 (CH_2) ppm; HREI-TOF: *m/z* calcd. for $C_{15}H_{15}N_3O_3S_3$ (M^+) 349.0377, found 349.0380.

Neuroprotection activity against $A\beta_{25–35}$-induced neurotoxicity in SH-SY5Y cells

SH-SY5Y cells were high passages from American Type Culture Collection (ATCC) and maintained at 37°C in a humidified atmosphere containing 5% CO_2. Cells were seeded into multiwell plates at a density of $2–2.5 \times 10^5$ cells per cm^3 in MEM/F12 medium (Gibco), supplemented with 10% heat-inactivated bovine calf serum, 100 U/cm^3 penicillin, and 100 μg/cm^3 streptomycin. Experiments were carried out 24 h after cells were seeded. Stock solution of $A\beta_{25–35}$ (Sigma, 1 mM) was prepared in phosphate buffer saline (PBS) with 4% dimethylsulfoxide (DMSO) and stored at −20°C, and diluted to 0.1 mM with PBS before application to cultures. All the test compounds were dissolved in DMSO to 10 mM as a stock solution, stored at −20°C, and diluted with MEM/F12 medium before usage. After pretreatment with the compounds for 2 h, 10 μM $A\beta_{25–35}$ were added to SH-SY5Y cell cultures for 24 h. Assays for cell viability were performed 24 h after cultured in fresh medium.

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