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Graphical Abstract

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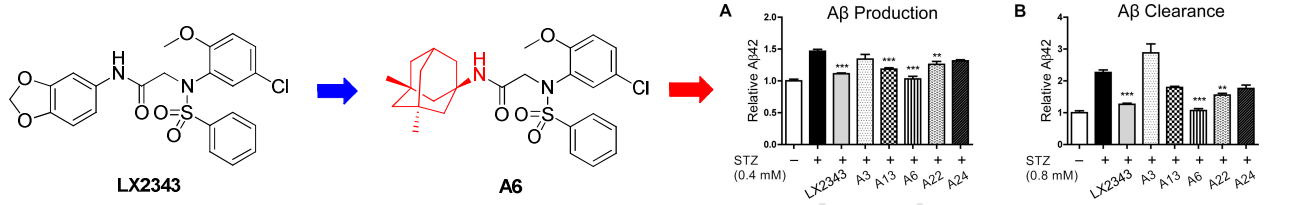

EC_{50}: 15.8 μM

EC_{50}: 0.22 μM

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Design, synthesis and biological evaluation of LX2343 derivatives as neuroprotective agents for the treatment of Alzheimer's disease

Guanglong Sun[1,2,#], Junwei Wang[1,#], Xiaodan Guo[2], Min Lei[2], Yinan Zhang[1], Xiachang Wang[1], Xu Shen[1,*], Lihong Hu[1,2,*]

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ABSTRACT

A series of LX2343 derivatives were designed, synthesized and evaluated as neuroprotective agents for Alzheimer's disease (AD) in vitro. Most of the compounds displayed potent neuroprotective activities. Especially for compound **A6**, exhibited a remarkable EC_{50} value of 0.22 μM. Further investigation demonstrated that compound **A6** can significantly reduce Aβ production and increase Aβ clearance, and alleviate Tau hyperphosphorylation. Most importantly, compound **A6** could ameliorate learning and memory impairments in APP/PS1 transgenic mice. The present study evidently showed that compound **A6** is a potent neuroprotective agent and might serve as a promising lead candidate for the treatment of Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder in the elderly population characterized by irreversible cognitive impairment, disorientation and personality changes, and ultimately causing death [1]. The apoptosis of neurons, the accumulation of amyloid β (Aβ) plaques and the formation of neurofibrillary tangles (NFTs) in the brain are the typical hallmarks of AD [2]. There is approximately 36 million people suffering from AD worldwide, and the figure is projected to grow to 114 million by 2050 [3,4]. Due to complex nature and multitude of factors potentially involved in pathogenesis, many aspects of AD are not yet fully known, to date, an effective treatment for this disease has not been found.

Currently, the therapeutic options for the treatment of AD are limited to three acetylcholinesterase (AChE) inhibitors donepezil, rivastigmine, galantamine and one *N*-methyl-D-aspartate receptor antagonist, memantine [5,6]. These drugs are only able to treat symptoms of the disease by improving cognitive, behavioral and functional impairments. However, they do little to stop or reverse the progression. The consecutive failures in clinical trials for dozens of anti-AD agents suggested that the agent targeting single target might not work effectively on this complicated pathogenesis [7,8]. Several factors including low levels of neurotransmitter acetylcholine (ACh), oxidative stress (OS), dyshomeostasis of biometals, the aggregation of β-amyloid peptide and hyperphosphorylation of tau protein have been considered to play significant roles in the pathogenesis of AD [9-11]. Therefore, a new strategy is urgently needed for the discovery of anti-AD drugs.

Recent evidence indicates that failing to repair the damaged neurons may be the fundamental reason [12-15]. Neuroprotection is a valuable tool of modern medicine to potentially combat or slow down the progression of AD [16-22]. Therefore, the successful protection of neuronal cells from damage may potentially prevent AD [23-29]. In our previous work [30,31], the preliminary high throughput screening (HTS) lead to the discovery of a small molecule compound LX2343 which exhibited moderate neuroprotective activities with the EC_{50} value

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of 15.8 μM. Further investigation showed that LX2343 was able to effectively reverse the streptozocin (STZ)-induced neuronal apoptosis and tau hyperphosphorylation *in vitro* and *in vivo*, and this neuroprotective effect of LX2343 was ascribed to its function in the inhibition of OS and tauopathy. LX2343 alleviated Aβ levels by both activating its clearance and inhibiting its production under STZ-induced pathological conditions. Moreover, assays in APP/PS1 transgenic AD model mice verified the amelioration of AD-relevant pathogenesis and cognitive deficits by LX2343. These results demonstrated that LX2343 was a multifunctional agent which exhibits potential capability for ameliorating multi-abnormalities of AD pathogenesis. However, the neuroprotective activity of LX2343 was a little weak and the structure-activity relationship (SAR) has not been studied yet. In order to search novel and more potent neuroprotective agent, LX2343 was chosen as the lead compound for further structural optimization.

2. Results and discussion

2.1. Design of novel neuroprotective agent

LX2343 was obtained through high throughput screening and the structure-activity relationship was not clear. In this paper, we focus on the structural modifications of LX2343 to find more potent neuroprotective agent (Fig. 1). Firstly, considering size, electron density and structure type, different substituent groups were introduced to modify the part A, including aliphatic amine, aromatic amine and heterocycle-aromatic amine (Table 1). After the optimal R^1 group was determined, modification was continue on part B, such as introducing different substituents on the benzene ring or replacing sulfonyl with carbonyl (Table 2). Finally, part C was modified by introducing different substituents on the benzene ring or replacing the aromatic ring with aliphatic ring and chain (Table 3).

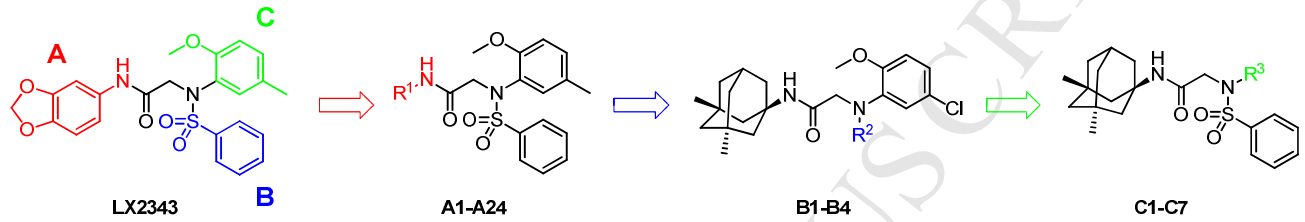
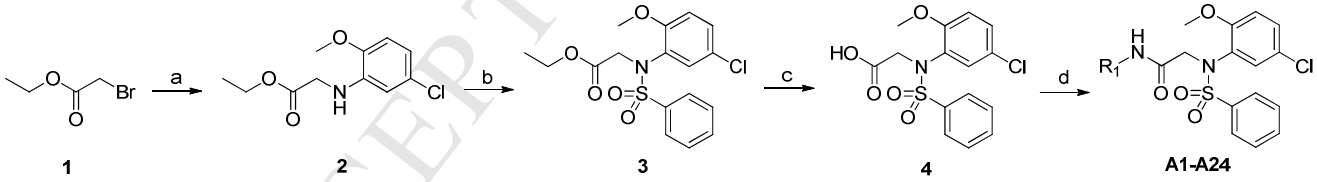


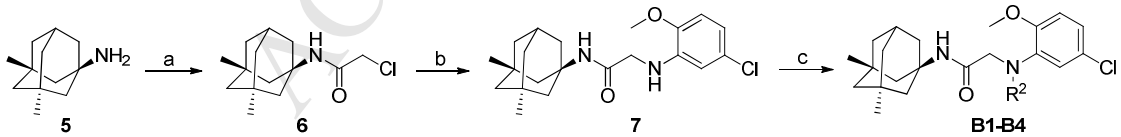
Fig. 1. Design of novel neuroprotective agents

2.2. Chemistry

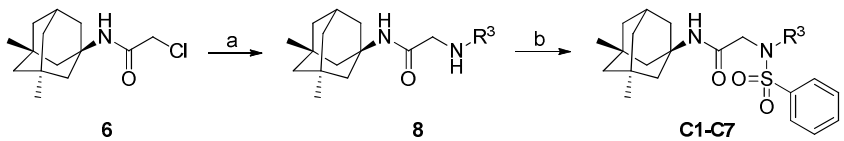
The synthetic routes for the designed thirty-five targeted compounds were depicted in Scheme 1-3. Firstly, reaction of commercially available ethyl bromoacetate and 5-chloro-2-methoxyaniline gave intermediate **2**. Sulfonylation of **2** with benzenesulfonyl chloride in pyridine using dimethylaminopyridine (DMAP) as catalytic agent provided the product **3**, which was further hydrolyzed to give the corresponding acid **4**. Then, it was activated with 2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluoro-phosphate (HATU) and subsequently coupled with different amines in the presence of *N*,*N*-diisopropylethylamine (DIPEA) to afford the target compounds **A1-A24** in moderate to good yields (Scheme 1). Compounds **B1-B4** were prepared according to Scheme 2. Treatment of 3,5-dimethyl amantadine with chloroacetyl chloride produced the corresponding amide **6** which reacted with 2-methoxy-5-chloro aniline giving intermediate **7**. Then, **7** was coupled with different sulfonyl chloride or acryl chlorides in the presence of DMAP to give **B1-B4**. The synthesis of compounds **C1-C7** is similar to that of **B1-B4**, coupling **6** with different amines and then reaction with benzene sulfonyl chloride gave the target compounds (Scheme 3). All the target compounds were purified by chromatographic techniques (see the experiment section for details) and structurally characterized by their spectroscopic data (^{1}H-NMR, ^{13}C-NMR, MS and HRMS).



Scheme 1. Reagents and conditions: (a) 5-chloro-2-methoxyaniline, DIPEA, CH_3CN, reflux, 10 h, 90%; (b) benzenesulfonyl chloride, DMAP, Py, r.t., 6 h, 87%; (c) NaOH, H_2O/THF/MeOH, r.t., 1 h, 94%; (d) amines, HATU, DIPEA, r.t., 1 h, 46-94%.



Scheme 2. Reagents and conditions: (a) chloroacetyl chloride, TEA, CH_2Cl_2, r.t., 2 h, 99%; (b) 2-methoxy-5-chloro aniline, Et_3N, NaI, EtOH, reflux, 10 h, 54%; (c) sulfonyl chlorides or acryl chlorides, DMAP, Py, r.t., 10 h, 66-90%.



Scheme 3. Reagents and conditions: (a) amines, Et_3N, NaI, EtOH, reflux, 10 h; (b) benzene sulfonyl chloride, DMAP, Py, r.t., 10 h, 18-68% (two steps).

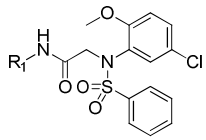
2.3. Inhibition of apoptosis in SH-SY5Y cells induced by STZ

The protective activity of the thirty-five compounds against STZ-induced apoptosis was evaluated in SH-SY5Y cells and the results were shown in Table 1-3. Most of the compounds showed potent neuroprotection against STZ-induced cells death. On the basis of these results, following SAR has been derived to analyze the influence of the modifications on part A、part B and part C.

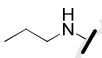
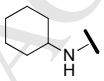
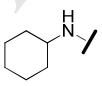
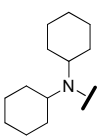
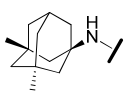
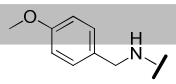
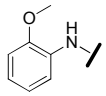
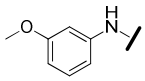
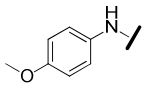
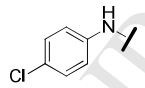
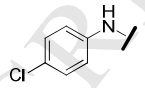
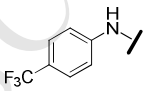
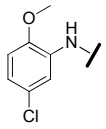
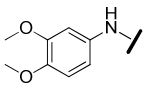
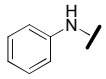
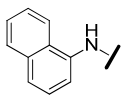
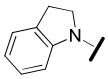
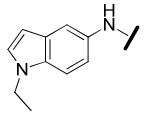
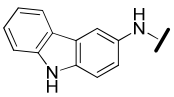
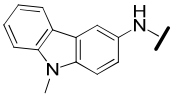
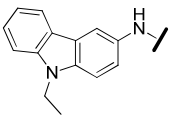
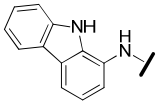
When changing the R^1 substituent, the amide compounds with aliphatic groups showed similar potency to LX2343 (EC_{50}: 15.80 μM), except for compound **A6** which bearing a memantine group. It exhibited a great increase in neuroprotection potency with the EC_{50} value of 0.22 μM. Aromatic amine substituted compounds **A12** and **A13** which bearing an electron-withdrawing group at the para-position of the benzene ring displayed higher potency than LX2343. Compounds with hetero-aromatic ring (**A19**-**A24**) also showed potent activity, especially for compound **A22**, it displayed the most potent activity with a significant EC_{50} value of 0.25 μM. However, the activities of **B1**-**B4** decreased a lot by changing the R^2 substituent, which means that benzenesulfonyl is very important for the activity and not suitable for modification any more. The results of **C1**-**C7** showed that the chlorine on aromatic ring is the necessary group to maintain the activity. The location of chlorine also affect the activity, among which, meta-position > ortho-position > para-position (**C4** > **C3** > **C5**). In addition, introducing a methyl on the para-position can further improve the activity, for example, **C7** showed stronger activity than its parent compound **C3**. In general, the results of modifications on part B and part C are not ideal, indicating that these two parts are not suitable for structural modification. The good news is that in the modification of part A, several compounds with high potency were obtained. Considering the potency and the structure types, compounds **A3**, **A6**, **A13**, **A22** and **A24** were selected for further investigation.

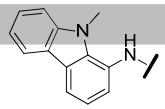
Table 1

The structure and the effects of compounds **A1**-**A24** on STZ-induced cell death in SH-SY5Y cells.



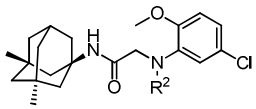
A1-A24

Compd	NHR^1/ R^1NR^1	EC_{50} (μM)[a]
A1		> 20
A2		> 20
A3		14.52 ± 1.08
A4		17.55 ± 1.45
A5		14.26 ± 1.72
A6		0.22 ± 0.02
A7		> 20
A8		15.50 ± 1.28
A9		17.60 ± 1.35
A10		16.20 ± 1.10
A11		> 20
A12		8.21 ± 0.54
A13		3.75 ± 0.28
A14		> 20
A15		> 20
A16		> 20
A17		17.43 ± 2.06
A18		> 20
A19		2.22 ± 0.25
A20		2.75 ± 0.31
A21		1.32 ± 0.10
A22		0.25 ± 0.02
A23		6.56 ± 0.43

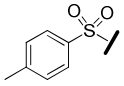
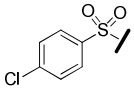
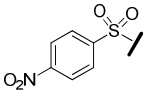
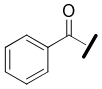
A24		3.18 ± 0.21
LX2343		15.80 ± 1.81

[a]EC_{50} was measured by the MTT assay with six concentrations (1, 2.5, 5, 10, 15, 20 μM). Data shown are means ± SEM.

Table 2
The structure and the effects of compounds on STZ-induced cell death in SH-SY5Y cells.

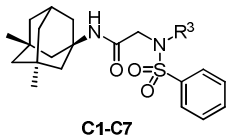


B1-B4

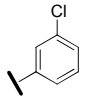
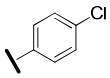
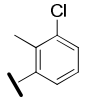
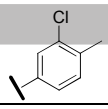
Compd	R^2	EC_{50} (μM)[a]
B-1		> 20
B-2		> 20
B-3		> 20
B-4		> 20

[a]EC_{50} was measured by the MTT assay with six concentrations (1, 2.5, 5, 10, 15, 20 μM).

Table 3
The structure and the effects of compounds on STZ-induced cell death in SH-SY5Y cells.



C1-C7

Compd	R^3	EC_{50} (μM)[a]
C-1		> 20
C-2		> 20
C-3		16.11 ± 1.88
C-4		12.30 ± 1.44
C-5		> 20
C-6		> 20
C-7		8.86 ± 0.49

[a]EC_{50} was measured by the MTT assay with six concentrations (1, 2.5, 5, 10, 15, 20 μM). Data shown are means ± SEM.

2.4. Inhibition of Aβ production and promotion of Aβ clearance

In order to investigate the potential to alleviate Aβ burden under pathological conditions by LX2343 derivatives, STZ was used as a stimulator and ELISA assays were performed in HEK293-APP_{sw} cells. ELISA results showed that LX2343 derivatives can effectively antagonize Aβ deposition in HEK293-APP_{sw} cells at the concentration of 20 μM. Among these derivatives, compound **A6** exhibited the most potent inhibition of Aβ production (Fig. 2A). Aβ in the brain exists in a dynamic equilibrium of Aβ production and clearance, so the potential effect of LX2343 derivatives on exogenous Aβ clearance was also investigated in SH-SY5Y cells. The results indicated that compounds **A6**, **A13**, **A22** and **A24** can enhance exogenous Aβ clearance, and the best effect was found for compound **A6** which was better than LX2343 (Fig. 2B). These results suggested that our compounds could effectively inhibit STZ-induced Aβ production and promote Aβ clearance.

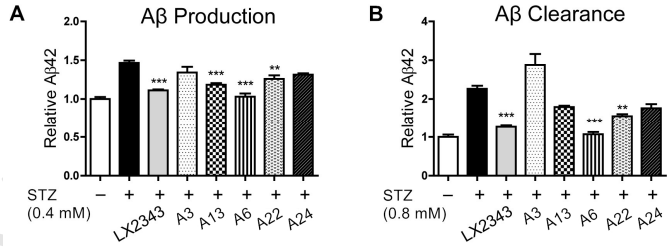


Fig. 2. LX2343 and its analogues effectively reversed STZ-induced Aβ accumulation and promoted Aβ clearance. (A) ELISA assays of compounds-induced Aβ decrease in HEK293-APP_{sw} cells. (B) ELISA results indicated that compounds increased Aβ clearance in SH-SY5Y cells (one-way ANOVA, Dunnett's multiple comparison test. $n = 3$. $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ vs STZ). All data were obtained from three independent experiments and are presented as the mean ± SEM.

2.5. Inhibition of Tau hyperphosphorylation

Considering the association of OS with tauopathy, we examined the potential of compounds **A3**, **A6**, **A13** and **A22** (at 20 μM) to suppress Tau hyperphosphorylation at residue Ser396 in SH-SY5Y cells. As expected, the results indicated that compounds **A6** and **A13** can efficiently attenuate the STZ-induced elevation of Tau phosphorylation (Fig. 3). Among these compounds, **A6** showed the strongest activity to inhibit the Tau hyperphosphorylation. Thus, compound **A6** was selected for further in vivo evaluation.

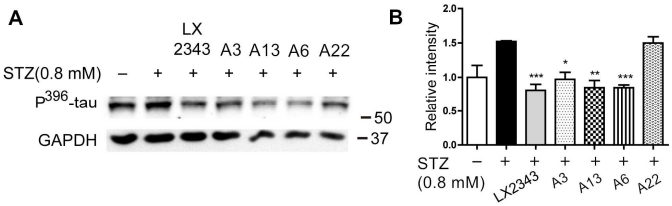


Fig. 3. LX2343 and its analogues ameliorated tau pathology. Western blot and quantification results demonstrated that compounds reduced tau phosphorylation at sites of serine 396 in SH-SY5Y cells (one-way ANOVA, Dunnett's multiple comparison test, $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ versus STZ). All values were presented as the

mean ± SEM (n = 3). GAPDH was used as the loading control in the Western blot assays. Data were obtained from three independent experiments.

2.6. In vivo anti-AD activity

APP/PS1 mice which express chimeric human Swedish mutant APP and a mutant human presenilin 1 protein are widely used as an effective animal model for AD dementia [32]. In this model, it is evaluated the amelioration of memory impairment by compound **A6** using the Morris Water Maze (MWM) test.

As depicted in Fig. 4, the results revealed that in six-day training trials, the path lengths and escape latencies used to find the platform for APP/PS1 transgenic mice were remarkably longer than those for non-transgenic mice, while 30 mg/kg compound **A6** administration obviously antagonized the prolonged path lengths and escape latencies on the sixth day (Figure 4A, 4B). In the probe trial assay, the compound **A6**-administered transgenic mice crossed over the hidden location of the platform more frequently compared with the vehicle-administered transgenic mice (Figure 4C, 4D). The animal experiments were carried out with two different doses of compound **A6**, 15 and 30 mg/kg. More obvious improvement was detected in memory and learning in the high-dose treatment group, it indicated the dose-dependent effect of compound **A6** in vivo. Additionally, there are no apparent changes in body weight, liver function or swimming speed of the tested mice after the treatment of compound **A6** (data not shown).

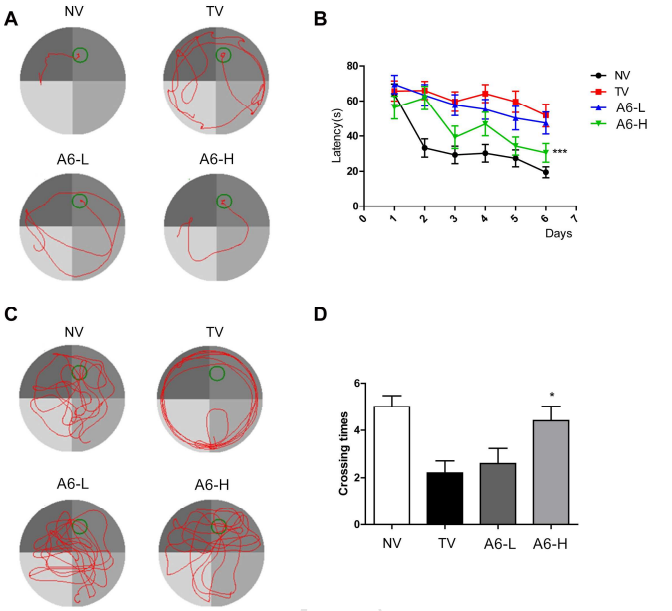


Fig. 4. Compound **A6** effectively improved learning and memory impairments in APP/PS1 transgenic mice. Behavioral tests and quantitative analyses of the APP/PS1 transgenic mice. (A) Representative tracing graphs showing the training trials. (B) Escape latency during the platform trials in the MWM tests (two-way ANOVA with repeated measures over time: treatment, $P < 0.0001$; time, $P < 0.0001$; treatment×time. ***$P < 0.001$ vs TV. n = 10). (C) Representative tracing graphs of the probe trials. (D) Times of the platform crossings in the probe trials (t test, *$P < 0.05$ vs TV. n = 10). NV: non-transgenic mice administered vehicle, TV: Transgenic mice administered vehicle, **A6**: transgenic mice administered with 15 $mg.kg^{-1}.d^{-1}$ (**A6-L**) and 30 $mg.kg^{-1}.d^{-1}$ (**A6-H**). Values are expressed as the mean±SEM.

3. Conclusions

In conclusion, to develop effective drugs for the treatment of Alzheimer's disease (AD), a series of LX2343 derivatives were designed, synthesized and evaluated. Among all the tested compounds, compounds **A6** and **A22** showed very potent neuroprotective effect with the EC_{50} values of 0.22 and 0.17 μM, respectively, which were much stronger than LX2343 (EC_{50}: 15.80 μM). ELISA assays and western blot results demonstrated that compound **A6** can significantly reduce Aβ production, increase Aβ clearance and alleviate Tau hyperphosphorylation. In addition, administration of compound **A6** in APP/PS1 transgenic mice also effectively improved learning and memory impairments. Taking together, all these results suggest that compound **A6** could be considered as a potential neuroprotective agent for the treatment of AD.

4. Experimental section

4.1. Materials and physical measurements

All cell culture reagents were purchased from Gibco (Invitrogen, USA). 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), STZ, wortmannin, SB216763 and chloroquine were purchased from Sigma-Aldrich company (USA). All chemical reagents were purchased from Sinopharm Chemical Reagent Co., Ltd. (China), Alfa Aesar, Adamas-beta, J&K and TCI. All solvents were used without further purifications. Reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF254 (Yantai, China) plates and the spots were detected under UV light (254 nm). Column chromatography was performed on silica gel (200-300 mesh) from Yantai (China). Melting point were recorded on a WRS-1B melting point apparatus and uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in DMSO-d_6 or $CDCl_3$ solutions using an AVANCE III 400 spectrometer. Chemical shifts are reported in δ scale (ppm) relative to internal tetramethylsilane (TMS), J values are given in Hertz, and spin multiplicities are expressed as s (singlet), d (doublet), t (triplet), or m (multiplet). Low and high-resolution mass spectra were obtained in the ESI mode.

4.2. Chemistry

*4.2.1. General procedure for the synthesis of **2***

To a stirred solution of ethyl bromoacetate **1** (4.0 g, 24 mmol) and DIPEA (4.01 g, 24 mmol) in CH_3CN (100 mL) was added 5-chloro-2-methoxyaniline (3.14 g, 20 mmol) at room temperature. The mixture was heated to reflux for 10 h, and TLC indicated that the reaction was completed. Then the reaction mixture was evaporated to dryness under vacuum. The obtained residue was further purified by silica gel chromatography (petroleum ether (PE)/ethyl acetate (EtOAc) = 5/1) to give **2** as a yellow oil (Yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.62 (s, 2H), 6.40 (s, 1H), 4.90 (t, J = 5.2 Hz, 1H), 4.23 (q, J = 7.2 Hz, 2H), 3.84 (d, J = 5.2 Hz, 2H), 3.78 (s, 3H), 1.28 (t, J = 7.2 Hz, 3H); ESI-MS (m/z): 244.6 $[M+H]^+$; HRMS (ESI): calcd for $C_{11}H_{14}ClNO_3$ $[M+H]^+$ 244.0735, found 244.0729.

*4.2.2. General procedure for the synthesis of **3***

Benzenesulfonyl chloride (3.52 g, 20 mmol) was added dropwise to a solution of **2** (2.43 g, 10 mmol) and DMAP (0.61 g, 5 mmol) in pyridine (50 mL) at room temperature. The mixture was continuously stirred at room temperature for 6 h, and TLC indicated that the reaction was completed. Then the reaction was concentrated and diluted with CH_2Cl_2 (50 mL) and H_2O (50 mL). The aqueous layer was separated and the organic layer was

washed with saturated Na_2CO_3 solution (2 × 50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum. The residue was further purified by silica gel chromatography (PE/EtOAc = 3/1) to give **3** as a white solid (Yield 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.68 (d, J = 8.0 Hz, 2H), 7.55-7.59 (m, 2H), 7.46 (t, J = 8.0 Hz, 2H), 7.26 (dd, J = 8.8, 2.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.38 (s, 2H), 4.17 (q, J = 7.2 Hz, 2H), 3.37 (s, 3H), 1.26 (t, J = 7.2 Hz, 3H); ESI-MS (*m/z*): 384.6 $[M+H]^+$; HRMS (ESI): calcd for $C_{17}H_{18}ClNO_5S$ $[M+H]^+$ 384.0667, found 384.0668.

*4.2.3. General procedure for the synthesis of **4***

3 (3.83 g, 10 mmol) and NaOH (0.80 g, 20 mmol) was added to a mixed solution of H_2O/THF/MeOH (2/2/1) (20 mL) at room temperature. The mixture was continuously stirred at room temperature for 1 h, and TLC indicated that the reaction was completed. Then the reaction was concentrated and diluted with H_2O (15 mL). When the solution was acidified to pH 3-4 by hydrochloric acid, a large amount of white solid dissolve out. After filtered, the residue was washed with H_2O, and dried to afford **4** as a white solid (Yield 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 7.63-7.69 (m, 3H), 7.56 (t, J = 7.6 Hz, 2H), 7.39-7.41 (m, 2H), 6.98 (d, J = 9.6 Hz, 1H), 4.27 (s, 2H), 3.29 (s, 3H); ESI-MS (*m/z*): 356.7 $[M+H]^+$; HRMS (ESI): calcd for $C_{15}H_{14}ClNO_5S$ $[M+H]^+$ 356.0354, found 356.0350.

*4.2.4. General procedure for the synthesis of LX2343 and **A1-24***

To a stirred solution of **4** (355 mg, 1 mmol) and HATU (456 mg, 1.2 mmol) in CH_2Cl_2 (6 mL) was added DIPEA (155 mg, 1.2 mmol) and the appropriate amine (1 mmol) at room temperature. The mixture was continuously stirred for 1 h, and TLC indicated that the reaction was completed. Then the reaction mixture was concentrated and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was separated and the organic layer was washed with saturated Na_2CO_3 solution (2 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum to obtain the desired crude products. The appropriate compounds (LX2343 and **A1**-**24**) were obtained following purification by silica gel chromatography.

4.2.5. N-(benzo[d][1,3]dioxol-5-yl)-2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)acetamide (LX2343)

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.08 (s, 1H), 7.74-7.68 (m, 3H), 7.57 (t, J = 8.4 Hz, 2H), 7.33 (dd, J = 8.8, 2.4 Hz, 1H), 7.24 (d, J = 2.0 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 6.88 (d, J = 2.4 Hz, 1H), 6.85 (dd, J = 8.4, 2.0 Hz, 1H), 6.78 (d, J = 8.4 Hz, 1H), 5.97 (s, 2H), 4.21 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.9, 155.4, 147.9, 144.6, 137.5, 133.7, 131.7, 130.6, 130.0, 129.2 (3C), 128.1 (2C), 126.1, 113.9, 113.2, 108.2, 102.8, 101.4, 56.6, 55.3; ESI-MS (*m/z*): 475.5 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{19}ClN_2O_6S$ $[M+H]^+$ 475.0725, found 475.0729.

*4.2.6. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-propylacetamide (**A1**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70-7.60 (m, 3H), 7.52 (t, J = 7.7 Hz, 2H), 7.30 (dd, J = 8.9, 2.6 Hz, 1H), 6.93 (d, J = 2.6 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 4.10 (s, 2H), 3.63 (s, 3H), 3.24 (q, J = 6.9 Hz, 2H), 1.60-1.48 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 167.8, 155.0, 137.7, 133.4, 130.5, 130.2, 128.9 (2C), 128.7, 127.8 (2C), 125.7, 113.3, 55.8, 54.4, 41.2, 22.6, 11.3; ESI-MS (*m/z*): 397.3 $[M+H]^+$; HRMS (ESI): calcd for $C_{18}H_{21}ClN_2O_4S$ $[M+H]^+$ 397.0983, found 397.0996.

*4.2.7. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N,N-diethylacetamide (**A2**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 84%). ^{1}H NMR (400 MHz, CDCl3) δ (ppm): 7.73-7.68 (m, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.50-7.43 (m, 3H), 7.22 (dd, J = 8.8, 2.7 Hz, 1H), 6.69 (d, J = 8.9 Hz, 1H), 4.45 (s, 2H), 3.43 (s, 3H), 3.39 (q, J = 7.1 Hz, 2H), 3.29 (q, J = 7.1 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 166.3, 155.4, 140.2, 133.8, 133.2, 130.0, 129.3 (2C), 127.9, 127.5 (2C), 123.3, 114.1, 56.0, 50.8, 40.9, 40.6, 14.4, 13.2; ESI-MS (*m/z*): 411.5 $[M+H]^+$; HRMS (ESI): calcd for $C_{19}H_{23}ClN_2O_4S$ $[M+H]^+$ 411.1140, found 411.1152.

*4.2.8. N-(5-chloro-2-methoxyphenyl)-N-(2-oxo-2-(piperidin-1-yl)ethyl)benzenesulfonamide (**A3**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 92%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.73-7.65 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.50-7.41 (m, 3H), 7.22 (dd, J = 8.8, 2.7 Hz, 1H), 6.68 (d, J = 8.9 Hz, 1H), 4.46 (s, 2H), 3.52-3.42 (m, 4H), 3.38 (s, 3H), 1.68-1.60 (m, 4H), 1.55-1.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.6, 155.0, 139.6, 133.6, 132.5, 129.8, 128.5 (2C), 127.6 (2C), 127.3, 125.1, 112.4, 55.4, 51.2, 46.1, 43.1, 26.3, 25.4, 24.3; ESI-MS (*m/z*): 423.3 $[M+H]^+$; HRMS (ESI): calcd for $C_{20}H_{23}ClN_2O_4S$ $[M+H]^+$ 423.1140, found 423.1141.

*4.2.9. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-cyclohexylacetamide (**A4**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a brown solid (Yield 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.71-7.61 (m, 3H), 7.52 (t, J = 7.7 Hz, 2H), 7.29 (dd, J = 8.9, 2.6 Hz, 1H), 7.12 (d, J = 8.5 Hz, 1H), 6.89 (d, J = 2.6 Hz, 1H), 6.84 (d, J = 8.9 Hz, 1H), 4.08 (s, 2H), 3.78-3.68 (m, 1H), 3.66 (s, 3H), 1.92-1.82 (m, 2H), 1.78-1.68 (m, 2H), 1.66-1.56 (m, 1H), 1.45-1.29 (m, 2H), 1.28-1.10 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.7, 155.1, 137.7, 133.3, 130.3, 130.2, 128.9 (2C), 128.8, 127.9 (2C), 125.6, 113.3, 55.8, 54.5, 48.2, 32.8 (2C), 25.5, 24.7 (2C); ESI-MS (*m/z*): 437.6 $[M+H]^+$; HRMS (ESI): calcd for $C_{21}H_{25}ClN_2O_4S$ $[M+H]^+$ 437.1296, found 437.1288.

*4.2.10. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N,N-dicyclohexylacetamide (**A5**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.70 (d, J = 7.6 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.44-7.49 (m, 3H), 7.24 (dd, J = 8.8, 2.4 Hz, 1H), 6.70 (d, J = 8.8 Hz, 1H), 4.41 (s, 2H), 3.76-3.79 (m, 1H), 3.39 (s, 3H), 2.91-2.95 (m, 1H), 1.72-1.89 (m, 6H), 1.12-1.56 (m, 12H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.9, 155.1, 139.6, 133.5, 132.4, 129.8, 128.4 (2C), 127.6 (2C), 127.1, 124.9, 112.4, 57.3, 56.1, 55.3, 52.5, 31.5 (2C), 29.6 (2C), 26.5 (2C), 25.8 (2C), 25.3, 25.1; ESI-MS (*m/z*): 519.9 $[M+H]^+$; HRMS (ESI): calcd for $C_{27}H_{35}ClN_2O_4S$ $[M+H]^+$ 519.2079, found 519.2075.

*4.2.11. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide (**A6**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 94%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64-7.70 (m, 3H), 7.54 (t, J = 7.6 Hz, 2H), 7.31

(dd, *J* = 8.8, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.92 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 3.99 (s, 2H), 3.65 (s, 3H), 2.15-2.18 (m, 1H), 1.84 (d, *J* = 2.0 Hz, 2H), 1.67 (d, *J* = 11.2 Hz, 2H), 1.61 (d, *J* = 11.2 Hz, 2H), 1.41 (d, *J* = 12 Hz, 2H), 1.31 (d, *J* = 12 Hz, 2H), 1.13-1.22 (m, 2H), 0.87 (s, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.7, 155.1, 137.8, 133.3, 130.4, 130.1, 128.9 (3C), 127.9 (2C), 125.6, 113.3, 55.7, 55.0, 53.5, 50.5, 47.3 (2C), 42.5 (2C), 39.8, 32.3 (2C), 30.1, 30.0 (2C); ESI-MS (*m/z*) 517.8 [M+H]+; HRMS (ESI): calcd for $C_{27}H_{33}ClN_2O_4S$ $[M+H]^+$ 517.1922, found 517.1928.

*4.2.12. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(4-methoxybenzyl)acetamide (**A7**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.69-7.61 (m, 3H), 7.57 (t, *J* = 4.9 Hz, 1H), 7.52 (t, *J* = 7.7 Hz, 2H), 7.27 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.91-6.84 (m, 2H), 6.82 (d, *J* = 2.6 Hz, 1H), 6.74 (d, *J* = 8.9 Hz, 1H), 4.38 (d, *J* = 5.4 Hz, 2H), 4.15 (s, 2H), 3.81 (s, 3H), 3.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 167.6, 159.1, 155.0, 137.6, 133.4, 130.3, 130.2, 129.6, 129.1 (2C), 129.0 (2C), 128.7, 127.9 (2C), 125.6, 114.1, 113.2, 55.4, 55.3, 54.5, 43.1; ESI-MS (*m/z*) 475.8 $[M+H]^+$; HRMS (ESI): calcd for $C_{23}H_{23}ClN_2O_5S$ $[M+H]^+$ 475.1089, found 475.1092.

*4.2.13. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(2-methoxyphenyl)acetamide (**A8**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.18 (s, 1H), 8.29 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.71-7.65 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.53 (d, *J* = 2.6 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 7.28 (dd, *J* = 8.9, 2.6 Hz, 1H), 7.08 (td, *J* = 7.8, 1.6 Hz, 1H), 6.95 (t, *J* = 8.5 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 1H), 4.36 (s, 2H), 4.04 (s, 3H), 3.32 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.1, 154.4, 148.4, 138.3, 133.1, 132.7, 130.3, 128.7 (2C), 127.8 (2C), 127.5, 127.0, 125.3, 124.3, 120.9, 119.9, 112.8, 110.2, 56.0, 55.2, 54.3; ESI-MS (*m/z*): 461.2 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{21}ClN_2O_5S$ $[M+H]^+$ 461.0932, found 461.0940.

*4.2.14. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(3-methoxyphenyl)acetamide (**A9**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.12 (s, 1H), 7.72 (d, *J* = 7.9 Hz, 2H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.28-7.20 (m, 2H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.93-6.84 (m, 2H), 6.69 (d, *J* = 7.4 Hz, 1H), 4.21 (s, 2H), 3.81 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.0, 160.1, 155.2, 138.6, 137.4, 133.6, 130.5, 129.9, 129.7, 129.1 (2C), 129.0, 128.0 (2C), 126.0, 113.8, 112.0, 110.4, 105.6, 56.4, 55.4, 55.3; ESI-MS (*m/z*): 461.2 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{21}ClN_2O_5S$ $[M+H]^+$ 461.0932, found 461.0937.

*4.2.15. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(4-methoxyphenyl)acetamide (**A10**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.03 (s, 1H), 7.72 (d, *J* = 7.5 Hz, 2H), 7.67 (t, *J* = 7.4 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 7.31 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.93-6.84 (m, 4H), 4.21 (s, 2H), 3.80 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.8, 156.6, 155.2, 137.5, 133.6, 130.5, 130.4, 130.0, 129.1 (2C), 129.0, 128.0 (2C), 125.9, 121.6 (2C), 114.2 (2C), 113.7, 56.3, 55.4, 55.2; ESI-MS (*m/z*): 461.2 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{21}ClN_2O_5S$ $[M+H]^+$ 461.0932, found 461.0940.

*4.2.16. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(4-chlorophenyl)acetamide (**A11**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 7.68-7.74 (m, 3H), 7.51-7.60 (m, 4H), 7.31-7.35 (m, 3H), 6.93 (d, *J* = 8.8 Hz, 1H), 6.88 (d, *J* = 2.8 Hz, 1H), 4.22 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.1, 155.2, 137.3, 136.0, 133.7, 130.5, 130.0, 129.5, 129.1 (2C), 129.0 (3C), 128.0 (2C), 126.0, 124.6, 121.1 (2C), 113.8, 56.4, 55.3; ESI-MS (*m/z*): 465.4 $[M+H]^+$; HRMS (ESI): calcd for $C_{21}H_{18}Cl_2N_2O_4S$ $[M+H]^+$ 465.0437, found 465.0441.

*4.2.17. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(4-nitrophenyl)acetamide (**A12**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.54 (s, 1H), 8.24 (d, *J* = 9.1 Hz, 2H), 7.78-7.67 (m, 5H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.34 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 4.22 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.7, 155.2, 143.8, 143.2, 137.0, 133.8, 130.7, 129.8, 129.2 (2C), 129.0, 128.0 (2C), 126.3, 125.1 (2C), 119.2 (2C), 114.1, 56.7, 55.5; ESI-MS (*m/z*): 476.4 $[M+H]^+$; HRMS (ESI): calcd for $C_{21}H_{18}ClN_3O_6S$ $[M+H]^+$ 476.0678, found 476.0671.

*4.2.18. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(4-(trifluoromethyl)phenyl)acetamide (**A13**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 50%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.99 (s, 1H), 8.36 (d, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.69-7.73 (m, 3H), 7.39-7.63 (m, 8H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.38-4.45 (m, 4H), 3.38 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.4, 155.2, 140.5, 137.2, 133.7, 130.6, 129.8, 129.2 (2C), 129.0, 128.0 (2C), 126.3 (2C), 126.2 (2C), 126.1, 119.4 (2C), 113.9, 56.5, 55.4; ESI-MS (*m/z*): 499.4 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{18}ClF_3N_2O_4S$ $[M+H]^+$ 499.0701, found 499.0707.

*4.2.19. N-(5-chloro-2-methoxyphenyl)-2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)acetamide (**A14**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.21 (s, 1H), 8.39 (d, *J* = 2.4 Hz, 1H), 7.61-7.69 (m, 3H), 7.49-7.53 (m, 3H), 7.31 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.05 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 6.73 (d, *J* = 8.8 Hz, 1H), 4.36 (s, 2H), 4.05 (s, 3H), 3.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.3, 154.3, 147.0, 138.2, 133.2, 132.6, 130.4, 128.8 (2C), 127.9, 127.8 (2C), 127.5, 126.0, 125.3, 123.7, 119.7, 112.9, 111.0, 56.3, 55.3, 54.3; ESI-MS (*m/z*): 495.4 $[M+H]^+$; HRMS (ESI): calcd for $C_{22}H_{20}Cl_2N_2O_5S$ $[M+H]^+$ 495.0543, found 495.0545.

*4.2.20. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(3,4-dimethoxyphenyl)acetamide (**A15**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.05 (s, 1H), 7.68-7.75 (m, 3H), 7.58 (t, *J* = 8.0 Hz, 2H), 7.32-7.35 (m, 2H), 6.91-6.96 (m, 3H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.23 (s, 2H), 3.91 (s, 3H), 3.89 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.8, 155.2, 149.0, 146.1, 137.4, 133.6, 131.0, 130.4, 130.0, 129.1 (2C), 129.0, 128.0 (2C),

126.0, 113.7, 112.0, 111.3, 104.8, 56.3, 56.1, 55.9, 55.2; ESI-MS (*m/z*): 491.5 $[M+H]^+$; HRMS (ESI): calcd for $C_{23}H_{23}ClN_2O_6S$ $[M+H]^+$ 491.1038, found 491.1029.

*4.2.21. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N,N-diphenylacetamide (**A16**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.15 (s, 1H), 7.73-7.75 (m, 2H), 7.67-7.71 (m, 1H), 7.55-7.59 (m, 4H), 7.32-7.38 (m, 3H), 7.13-7.17 (m, 1H), 6.90-6.93 (m, 2H), 4.24 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.0, 155.3, 137.4, 133.6, 130.5, 129.9, 129.1 (3C), 129.0 (3C), 128.0 (2C), 126.0, 124.6, 119.8 (2C), 113.8, 56.4, 55.3; ESI-MS (*m/z*): 431.7 $[M+H]^+$; HRMS (ESI): calcd for $C_{21}H_{20}ClN_2O_4S$ $[M+H]^+$ 431.0827, found 431.0821.

*4.2.22. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(naphthalen-1-yl)acetamide (**A17**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 60%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.65 (s, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.91 (t, *J* = 6.8 Hz, 2H), 7.79-7.81 (m, 2H), 7.70-7.86 (m, 2H), 7.54-7.65 (m, 4H), 7.49 (t, *J* = 7.6 Hz, 1H), 7.34 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 1H), 4.36 (s, 2H), 3.57 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.8, 155.3, 137.4, 134.1, 133.6, 131.9, 130.5, 130.1, 129.2 (3C), 128.6, 128.1 (2C), 127.3, 126.6, 126.1, 126.0, 125.9, 125.6, 121.1, 120.6, 113.6, 56.0, 55.5; ESI-MS (*m/z*): 481.8 $[M+H]^+$; HRMS (ESI): calcd for $C_{25}H_{21}ClN_2O_4S$ $[M+H]^+$ 481.0983, found 481.0993.

*4.2.23. N-(5-chloro-2-methoxyphenyl)-N-(2-(indolin-1-yl)-2-oxoethyl)benzenesulfonamide (**A18**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 46%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.14 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 7.6 Hz, 2H), 7.56-7.61 (m, 2H), 7.48 (t, *J* = 7.6 Hz, 2H), 7.24 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.16-7.20 (m, 2H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 8.8 Hz, 1H), 4.56 (s, 2H), 4.18 (t, *J* = 8.4 Hz, 2H), 3.44 (s, 3H), 3.24 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ (ppm): 166.2, 155.5, 143.1, 140.3, 133.7, 133.3, 131.9, 130.1, 129.3 (2C), 128.0, 127.5 (2C), 127.4, 125.2, 123.9, 123.4, 116.3, 114.2, 56.0, 52.6, 46.7, 28.0; ESI-MS (*m/z*): 457.8 $[M+H]^+$; HRMS (ESI): calcd for $C_{23}H_{21}ClN_2O_4S$ $[M+H]^+$ 457.0983, found 457.0980.

*4.2.24. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(1-ethyl-1H-indol-5-yl)acetamide (**A19**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.12 (s, 1H), 7.83 (d, *J* = 1.2 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.26-7.34 (m, 3H), 7.14 (d, *J* = 3.2 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 6.48 (d, *J* = 3.2 Hz, 1H), 4.28 (s, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 3H), 148 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.8, 155.3, 137.6, 133.5, 133.4, 130.4, 130.1, 129.5, 129.1 (2C), 129.0, 128.6, 128.0 (2C), 127.9, 125.8, 115.6, 113.6, 112.9, 109.4, 101.2, 56.3, 55.3, 41.1, 15.4; ESI-MS (*m/z*): 498.7 $[M+H]^+$; HRMS (ESI): calcd for $C_{25}H_{24}ClN_3O_4S$ $[M+H]^+$ 498.1249, found 498.1240.

*4.2.25. N-(9H-carbazol-3-yl)-2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)acetamide (**A20**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.25 (s, 1H), 8.31 (s, 1H), 8.29 (d, *J* = 1.6 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 2H), 7.46 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.38 (d, *J* = 8.8 Hz, 1H), 7.33 (dd, *J* = 8.8, 2.8 Hz, 1H), 7.21-7.25 (m, 1H), 6.97 (d, *J* = 2.8 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.31 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.0, 155.3, 140.2, 137.5, 136.9, 133.6, 130.4, 130.0, 129.6, 129.1 (3C), 128.0 (2C), 126.1, 125.9, 123.5, 123.1, 120.5, 119.4, 119.3, 113.7, 112.5, 110.7 (2C), 56.3, 55.3; ESI-MS (*m/z*): 520.9 $[M+H]^+$; HRMS (ESI): calcd for $C_{27}H_{22}ClN_3O_4S$ $[M+H]^+$ 520.1092, found 520.1099.

*4.2.26. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(9-methyl-9H-carbazol-3-yl)acetamide (**A21**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.29 (s, 1H), 8.34 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.53-7.58 (m, 3H), 7.49 (t, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.28-7.33 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.8 Hz, 1H), 4.33 (s, 2H), 3.79 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.0, 155.2, 141.5, 138.4, 137.6, 133.6, 130.4, 130.2, 129.2, 129.1 (3C), 128.0 (2C), 126.0, 125.9, 122.8, 122.5, 120.5, 119.2, 118.8, 113.7, 112.5, 108.6, 108.5, 56.3, 55.3, 29.1; ESI-MS (*m/z*): 534.9 $[M+H]^+$; HRMS (ESI): calcd for $C_{28}H_{24}ClN_3O_4S$ $[M+H]^+$ 534.1249, found 534.1253.

*4.2.27. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(9-ethyl-9H-carbazol-3-yl)acetamide (**A22**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a light yellow solid (Yield 58%). ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 9.99 (s, 1H), 8.36 (d, *J* = 1.2 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.69-7.73 (m, 3H), 7.39-7.63 (m, 8H), 7.17 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 8.0 Hz, 1H), 4.38-4.45 (m, 4H), 3.38 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 165.8, 155.3, 140.4, 137.6, 137.4, 133.6, 130.4, 130.1, 129.2, 129.1 (3C), 128.0 (2C), 126.0, 125.9, 123.0, 122.7, 120.7, 119.2, 118.8, 113.7, 112.7, 108.5 (2C), 58.3, 55.3, 37.6, 13.8; ESI-MS (*m/z*): 548.7 $[M+H]^+$; HRMS (ESI): calcd for $C_{29}H_{26}ClN_3O_4S$ $[M+H]^+$ 548.1405, found 548.1416.

*4.2.28. N-(9H-carbazol-1-yl)-2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)acetamide (**A23**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 57%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.57 (s, 1H), 9.43 (s, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 7.99 (dd, *J* = 7.6, 0.8 Hz, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 2H), 7.41-7.49 (m, 2H), 7.35 (dd, *J* = 8.8, 2.4 Hz, 1H), 7.17-7.26 (m, 3H), 6.98 (d, *J* = 2.8 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 4.35 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 166.8, 155.2, 139.9, 137.2, 133.8, 133.0, 130.6, 130.0, 129.3, 129.2 (2C), 128.0 (2C), 126.2, 126.1, 125.9, 123.3, 121.0, 120.2, 119.4, 119.2, 118.7, 118.1, 113.8, 111.5, 56.4, 55.4; ESI-MS (*m/z*): 520.9 $[M+H]^+$; HRMS (ESI): calcd for $C_{27}H_{22}ClN_3O_4S$ $[M+H]^+$ 520.1092, found 520.1082.

*4.2.29. 2-(N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-(9-methyl-9H-carbazol-1-yl)acetamide (**A24**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a yellow solid (Yield 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 9.53 (s, 1H), 8.08 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.70 (t, *J* = 7.6 Hz, 1H), 7.58 (t, *J* = 7.6 Hz, 2H), 7.51 (t, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.37 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.30 (d, *J* = 7.6 Hz, 1H),

7.26 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 6.91 (d, *J* = 8.8 Hz, 1H), 4.39 (s, 2H), 4.07 (s, 3H), 3.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm): 168.4, 155.2, 141.9, 137.3, 135.8, 133.7, 130.6, 130.2, 129.2 (2C), 129.0, 128.0 (2C), 126.1, 126.0, 125.6, 124.7, 122.6, 120.1, 119.6, 119.4, 119.3, 119.1, 113.7, 108.8, 56.3, 55.3, 31.3; ESI-MS (*m/z*): 534.9 $[M+H]^+$; HRMS (ESI): calcd for $C_{28}H_{24}ClN_3O_4S$ $[M+H]^+$ 534.1249, found 534.1262.

4.2.30. General procedure for the synthesis of ***6***

To a stirred solution of 3,5-dimethyl amantadine **5** (1.79 g, 10 mmol) and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (50 mL) was added chloroacetyl chloride (0.98 mL, 13 mmol) at room temperature. The mixture was stirred at room temperature for 2 h, and TLC indicated that the reaction was completed. Then the mixture was washed with saturated Na_2CO_3 solution (2 × 50 mL), brine (50 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated under vacuum to give **6** as a brown solid (Yield 99%). ESI-MS (*m/z*): 256 $[M+H]^+$.

4.2.31. General procedure for the synthesis of ***7***

To a stirred solution of **6** (1.27 g, 5 mmol) and Et_3N (0.57 mL, 5 mmol) in EtOH (50 mL) was added 2-methoxy-5-chloro aniline (785 mg, 5 mmol) and NaI (745 mg, 5 mmol) at room temperature. The mixture was heated to reflux for 10 h, and TLC indicated that the reaction was completed. Then the mixture was filtered and the filtrate was evaporated to dryness under vacuum. The obtained residue was dissolved in ethyl acetate (50 mL) and washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum. The residue was further purified by silica gel chromatography (PE/EtOAc = 3/1) to give **7** as a white solid (Yield 54%). ESI-MS (*m/z*): 377 $[M+H]^+$.

4.2.32. General procedure for the synthesis of ***B1-B4***

The appropriate sulfonyl chlorides or acryl chlorides (1 mmol) was added dropwise to a solution of **7** (75 mg, 0.2 mmol) and DMAP (37 mg, 0.3 mmol) in pyridine (10 mL) at room temperature. The mixture was continuously stirred at room temperature for 10 h, and TLC indicated that the reaction was completed. Then the reaction was concentrated and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was separated and the organic layer was washed with saturated Na_2CO_3 solution (2 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum to obtain the desired crude products. The appropriate compounds (**B1**-**B4**) were obtained following purification by silica gel chromatography.

4.2.33. 2-(N-(5-chloro-2-methoxyphenyl)-4-methylphenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide ***(B-1)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.57 (d, *J* = 6.8 Hz, 2H), 7.29-7.33 (t, 3H), 6.86-6.95 (t, 3H), 3.96 (s, 2H), 3.69 (s, 3H), 2.46 (s, 3H), 2.15 (s, 1H), 1.81 (s, 2H), 1.65 (d, *J* = 10.8 Hz, 2H), 1.60 (d, *J* = 10.8 Hz, 2H), 1.39 (d, *J* = 10.8 Hz, 2H), 1.30 (d, *J* = 10.8 Hz, 2H), 1.15-1.16 (m, 2H), 0.86 (s, 6H); ESI-MS (*m/z*): 531 $[M+H]^+$.

4.2.34. 2-(4-chloro-N-(5-chloro-2-methoxyphenyl)phenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide ***(B-2)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.63 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.00 (s, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 6.79 (s, 1H), 3.99 (s, 2H), 3.66 (s, 3H), 2.16 (s, 1H), 1.83 (s, 2H), 1.64 (d, *J* = 12.0 Hz, 2H), 1.60 (d, *J* = 12.0 Hz, 2H), 1.39 (d, *J* = 12.0 Hz, 2H), 1.30 (d, *J* = 12.0 Hz, 2H), 1.13-1.21 (m, 2H), 0.87 (s, 6H); ESI-MS (*m/z*): 551 $[M+H]^+$.

4.2.35. 2-(N-(5-chloro-2-methoxyphenyl)-4-nitrophenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide ***(B-3)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a light yellow solid (Yield 84%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 8.36 (t, *J* = 1.2 Hz, 2H), 7.88 (t, *J* = 1.2 Hz, 2H), 7.34-7.35 (m, 1H), 7.06 (s, 1H), 6.87-6.88 (m, 1H), 6.63 (s, 1H), 4.03 (s, 2H), 3.61 (s, 3H), 2.05-2.16 (m, 1H), 1.83 (s, 2H), 1.62 (s, 4H), 1.17-1.37 (m, 6H), 0.87 (s, 6H); ESI-MS (*m/z*): 562 $[M+H]^+$.

4.2.36. N-(5-chloro-2-methoxyphenyl)-N-(2-(((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)amino)-2-oxoethyl)benzamide ***(B-4)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.34 (d, *J* = 7.6 Hz, 2H), 7.27 (t, *J* = 7.2 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 2H), 7.13-7.16 (dd, *J* = 8.8, 2.0 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 6.54 (s, 1H), 4.24-4.45 (m, 2H), 3.56 (s, 3H), 2.14 (t, *J* = 2.8 Hz, 1H), 1.84 (s, 2H), 1.67 (d, *J* = 12.0 Hz, 2H), 1.61 (d, *J* = 12.0 Hz, 2H), 1.39 (d, *J* = 12.0 Hz, 2H), 1.29 (d, *J* = 12.0 Hz, 2H), 1.12-1.21 (m, 2H), 0.86 (s, 6H); ESI-MS (*m/z*): 481 $[M+H]^+$.

4.2.37. General procedure for the synthesis of ***C1-C7***

To a stirred solution of **6** (1.27 g, 5 mmol) and Et_3N (0.57 mL, 5 mmol) in EtOH (50 mL) was added different amines (5 mmol) and NaI (745 mg, 5 mmol) at room temperature. The mixture was heated to reflux for 10 h, and TLC indicated that the reaction was completed. Then the mixture was filtered and the filtrate was evaporated to dryness under vacuum. The obtained residue was dissolved in ethyl acetate (50 mL) and washed with brine (2 × 50 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum. The residue was further purified by silica gel chromatography (PE/EtOAc = 3/1) to give **8** as a white solid.

Benzenesulfonyl chloride (1 mmol) was added dropwise to a solution of **8** (0.2 mmol) and DMAP (37 mg, 0.3 mmol) in pyridine (10 mL) at room temperature. The mixture was continuously stirred at room temperature for 10 h, and TLC indicated that the reaction was completed. Then the reaction was concentrated and diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was separated and the organic layer was washed with saturated Na_2CO_3 solution (2 × 10 mL), brine (10 mL) and dried over anhydrous Na_2SO_4. After filtered, the solvent was evaporated to dryness under vacuum to obtain the desired crude products. The appropriate compounds (**C1**-**C7**) were obtained following purification by silica gel chromatography.

4.2.38. 2-(N-cyclohexylphenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide ***(C-1)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.85 (d, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 2H), 6.39 (s, 1H), 3.84-3.90 (m, 1H), 3.62 (s, 2H), 2.16-2.19 (m, 1H), 1.88 (d, *J* = 1.6 Hz, 2H), 1.52-1.76 (m, 10H), 1.42 (d, *J* = 12.0 Hz, 2H), 1.26-1.32 (m, 6H), 1.14-1.23 (m, 2H), 0.88 (s, 6H); ESI-MS (*m/z*): 458 $[M+H]^+$.

4.2.39. N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)-2-(N-phenylphenylsulfonamido)acetamidee ***(C-2)***

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64 (t, J = 7.2 Hz, 1H), 7.57 (d, J = 7.2 Hz, 2H), 7.48 (t, J = 7.6 Hz, 2H), 7.34-7.36 (m, 3H), 7.05-7.08 (m, 2H), 6.28 (s, 1H), 4.08 (s, 2H), 2.13 (t, J = 2.8 Hz, 1H), 1.77 (s, 2H), 1.60 (d, J = 12.0 Hz, 2H), 1.54 (d, J = 12.0 Hz, 2H), 1.37 (d, J = 12.0 Hz, 2H), 1.28 (d, J = 12.0 Hz, 2H), 1.11-1.19 (m, 2H), 0.85 (s, 6H); ESI-MS (*m/z*): 453 $[M+H]^+$.

*4.2.40. 2-(N-(2-chlorophenyl)phenylsulfonamido)-N-((1r,3R,5S, 7r)-3,5-dimethyladamantan-1-yl)acetamide (**C-3**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a light yellow solid (Yield 18%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65-7.72 (m, 3H), 7.48-7.56 (m, 3H), 7.31-7.35 (m, 1H), 7.23-7.27 (m, 1H), 6.94 (dd, J = 8.0, 1.6 Hz, 1H), 6.79 (s, 1H), 3.89-3.90 (m, 2H), 2.14-2.17 (m, 1H), 1.86 (d, J = 2.0 Hz, 2H), 1.69 (d, J = 12.0 Hz, 2H), 1.65 (d, J = 12.0 Hz, 2H), 1.40 (d, J = 12.0 Hz, 2H), 1.30 (d, J = 12.0 Hz, 2H), 1.12-1.22 (m, 2H), 0.86 (s, 6H); ESI-MS (*m/z*): 487 $[M+H]^+$.

*4.2.41. 2-(N-(3-chlorophenyl)phenylsulfonamido)-N-((1r,3R,5S, 7r)-3,5-dimethyladamantan-1-yl)acetamide (**C-4**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 35%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.64 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 7.6 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.27-7.33 (m, 2H), 7.10 (s, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.17 (s, 1H), 4.05 (s, 2H), 2.12 (t, J = 2.8 Hz, 1H), 1.76 (s, 2H), 1.59 (d, J = 11.6 Hz, 2H), 1.54 (d, J = 11.6 Hz, 2H), 1.37 (d, J = 11.6 Hz, 2H), 1.28 (d, J = 11.6 Hz, 2H), 1.10-1.18 (m, 2H), 0.84 (s, 6H); ESI-MS (*m/z*): 487 $[M+H]^+$.

*4.2.42. 2-(N-(4-chlorophenyl)phenylsulfonamido)-N-((1r,3R,5S, 7r)-3,5-dimethyladamantan-1-yl)acetamide (**C-5**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 50%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65 (t, J = 7.2 Hz, 1H), 7.58 (d, J = 7.2 Hz, 2H), 7.49 (t, J = 7.6 Hz, 2H), 7.32 (d, J =8.8 Hz, 2H), 7.02 (d, J =8.8 Hz, 2H), 6.17 (s, 1H), 4.05 (s, 2H), 2.13-2.15 (m, 1H), 1.77 (d, J =1.2 Hz, 2H), 1.59 (d, J = 12.4 Hz, 2H), 1.54 (d, J = 12.4 Hz, 2H), 1.37 (d, J = 12.4 Hz, 2H), 1.29 (d, J = 12.4 Hz, 2H), 1.12-1.19 (m, 2H), 0.86 (s, 6H); ESI-MS (*m/z*): 487 $[M+H]^+$.

*4.2.43. 2-(N-(3-chloro-2-methylphenyl)phenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide (**C-6**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 20%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.67 (d, J = 8.0 Hz, 3H), 7.54 (t, J = 8.0 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.06 (t, J = 8.0 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.37 (s, 1H), 4.12 (d, J = 16.4 Hz, 1H), 3.83 (d, J = 16.4 Hz, 1H), 2.37 (s, 3H), 2.17 (s, 1H), 1.84 (s, 2H), 1.67 (d, J = 12.0 Hz, 2H), 1.62 (d, J = 12.0 Hz, 2H), 1.41 (d, J = 12.0 Hz, 2H), 1.31 (d, J = 12.0 Hz, 2H), 1.14-1.22 (m, 2H), 0.87 (s, 6H); ESI-MS (*m/z*): 501 $[M+H]^+$.

*4.2.44. 2-(N-(3-chloro-4-methylphenyl)phenylsulfonamido)-N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)acetamide (**C-7**)*

The product was purified by flash chromatography (PE/EtOAc = 3/1) to give a white solid (Yield 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.66 (t, J = 7.2 Hz, 1H), 7.60 (d, J = 7.2 Hz, 2H), 7.52 (t, J = 7.2 Hz, 2H), 7.20 (d, J = 8.0 Hz, 1H), 7.06 (d, J = 2.0 Hz, 1H), 6.86 (dd, J = 8.0, 2.0 Hz, 1H), 6.21 (s, 1H), 4.02 (s, 1H), 2.38 (s, 3H), 2.13-2.16 (m, 1H), 1.79 (d, J = 2.0 Hz, 2H), 1.61 (d, J = 12.0 Hz, 2H), 1.56 (d, J = 12.0 Hz, 2H), 1.40 (d, J = 12.0 Hz, 2H), 1.29 (d, J = 12.0 Hz, 2H), 1.12-1.20 (m, 2H), 0.86 (s, 6H); ESI-MS (*m/z*): 501 $[M+H]^+$.

4.3. Biological activity assay

4.3.1. Cell culture

SH-SY5Y cells were grown in a mixture (1:1) of Dulbecco's modified Eagle's medium and Ham's F-12 (DMEM/F12) supplemented with 10% fetal bovine serum (FBS) and 100 unit/mL penicillin-streptomycin. HEK293 cells expressing APP Swedish mutant$^{K595N/M596L}$ (HEK293-APP_{sw}) (kindly provided by Prof Gang PEI, Shanghai Institutes for Biological Sciences, China) were grown in DMEM containing 10% FBS and 100 unit/mL penicillin-streptomycin. All cells were cultured in a humidified incubator with 5% CO_2 at 37 °C.

4.3.2. Neuroprotection activity on SH-SY5Y

Potential neuroprotective activity was evaluated in human neuroblastoma SH-SY5Y cells treated with STZ. The compounds were pre-dissolved in DMSO and diluted in medium to at least five required concentrations. Viability of the cultured cells was determined by assaying the reduction of MTT to formazan. SH-SY5Y cells were seeded overnight in 48-well plates at a density of 10^5 cells/well in 100 μL medium. Cells were then incubated with different concentrations of compounds (5, 10 and 20 μM) and STZ (0.8 mM for SH-SY5Y cells) for 24 h and washed twice with PBS, followed by addition of MTT (0.5 mg/mL). After incubation at 37 °C for 4 h, 200 μL DMSO was added to dissolve the formazan crystals, and absorbance at 490 nm was measured using an M5 spectrophotometer (Molecular Devices, Sunnyvale, CA, USA).

4.3.3. Intracellular Aβ production and Aβ clearance assay

ELISA assay was used to evaluate the inhibitory activity against STZ-induced Aβ production in HEK293-APP_{sw} cells. Intracellular Aβ clearance in SH-SY5Y cells was detected according to the Landreth approach. These experiments were carried as previously described [30].

4.3.4. Immunohistochemistry assay

Immunohistochemistry assays were performed to detect the expression of P^{396}-Tau protein. These experiments were carried as previously described [31].

4.3.5. Animal experiments

All animal experiments were performed according to the Institutional Ethical Guidelines of Shanghai Institute of Materia Medica, Chinese Academy of Sciences, on animal care. These experiments were carried as previously described [30].

4.3.6. Statistical analysis

Data are reported as the mean ± SEM. The significant difference between multiple treatments and the control was analyzed using a one-way ANOVA with Dunnett's post-test. *P* values less than 0.05 were considered statistically significant.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at……

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