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Research paper

Novel ferulic amide derivatives with tertiary amine side chain as acetylcholinesterase and butyrylcholinesterase inhibitors: The influence of carbon spacer length, alkylamine and aromatic group

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ABSTRACT

Based on our recent investigations on chalcone derivatives as AChE inhibitors, a series of ferulic acid (FA) tertiary amine derivatives similar to chalcone compounds were designed and synthesized. The results of bioactivity evaluation revealed that most of new synthesized compounds had comparable or more potent AChE inhibitory activity than the control drug Rivastigmine. The alteration of carbon chain linking tertiary amine groups and ferulic acid scaffold markedly influenced the inhibition activity against AChE. Among them the inhibitory activity of compound **6d** (IC_{50}: 0.71 ± 0.09 μmol/L) and **6e** (IC_{50}: 1.11 ± 0.17 μmol/L) was equal to 15-fold and 9-fold than that of Rivastigmine against AChE (IC_{50}: 10.54 ± 0.86 μmol/L), respectively. Moreover, compound **6d** shows the highest selectivity for AChE over butyrylcholinesterase(BuChE) (ratio: 18.3). The kinetic study suggested that compound **6d** revealed a mixed-type inhibition against AChE. The result of molecular docking showed that compound **6d** combines to AChE with three amino acid sites(Trp84, Tyr334 and Trp279), while combines to BuChE with two amino acid sites (Tyr67 and Gly66) in enzyme domains, respectively. Compound **6d** might act as a potential agent for the treatment of Alzheimer's diseases (AD).

1. Introduction

Chalcone, a special natural product containing α,β-unsaturated carbonyl group, is thought as a reasonable scaffold to develop novel drugs via structure modification [1–3]. AChE inhibitors from natural products or their derivatives are considered as possible new resources for the treatment of Alzheimer's diseases (AD). In our laboratory more than one hundred Mannich base derivatives originated from natural products were screening for the bioactivity in inhibiting AChE in the past several years. Fortunately Flavokawain Mannich base derivatives containing chalcone scaffold were discovered with potent AChE inhibiting effect two years ago [4]. Afterwards, a lot of chalcone nitrogen-containing derivatives were synthesized and confirmed as potent AChE inhibitors in our further investigations [5–7]. According to these results, it seemed that the presence of an α,β-unsaturated carbonyl group in chalcone scaffold was essential for AChE inhibitory activity.

Ferulic acid, a natural product containing α,β-unsaturated carbonyl group, had versatile application prospects in medicine [8–10]. In the present investigation, a series of ferulic acid benzamide derivatives coupled with tertiary amines side chain were synthesized, and evaluated the biological activity in inhibiting AChE and BuChE. In order to explore whether the benzamide groups were essential for the bioactivity, some ferulic acid ester or free ferulic acid derivatives were synthesized and evaluated, compared with that of ferulic acid benzamide derivatives (Fig. 1). For the purpose of exploring the inhibition profile and mechanism, enzyme kinetic and molecular docking studies were carried out.

2. Results and discussion

2.1. Chemistry

In the beginning the amide derivative of ferulic acid (compound

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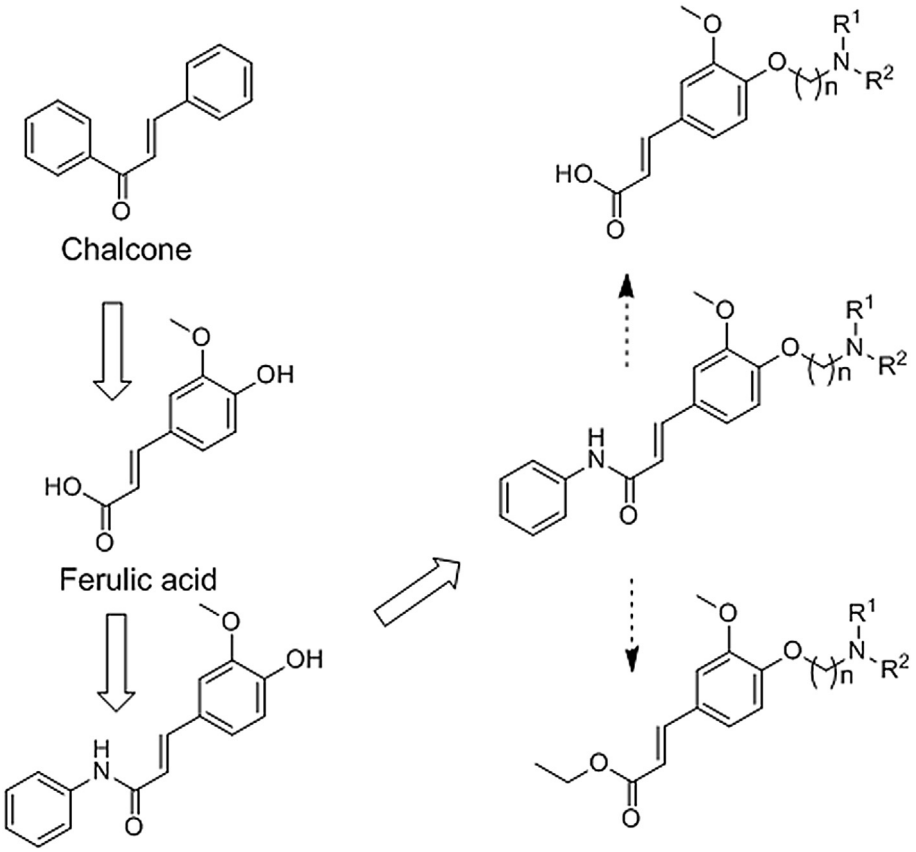


Fig. 1. Design strategy of the ferulic acid derivatives.

5) was planned to synthesize from ferulic acid and phenylamine directly, but only poor-yield product was gained. Then it was synthesized from ferulic acid chloride as the intermediate, but the impurity of the final product is not easy to remove. So new synthesis route was applied to prepared acetyl ferulic acid(compound **2**) firstly [11], and then acetyl ferulic acid chloride (compound **3**) was synthesized as an intermediate to gain compound **4** with previous reported method [12,13]. Finally, the acetyl group was hydrolyzed by ammonium hydroxide at room temperature to achieve compound **5** with a good yield. The synthesis route above is summarized in Scheme 1.

Compounds **2b-2e** were generated by compound **5** with four commercially available compounds (chloroethyldimethylamine hydrochloride, chloroethyldiethylamine hydrochloride, chloroethylpiperidine hydrochloride, or chloroethylpyrrolidine hydrochloride) in the presence of K_2CO_3 and NaI. Then compounds **3b-8e** were synthesized from compounds **3a-8a** which were prepared from compound **5** with different dibromoalkanes (Scheme 1).

In order to further investigate the influence of benzamide group in inhibiting AChE, the derivatives of four compounds possessing higher AChE inhibitory activity (compounds **6c, 7c, 6d** and **6e**) were synthesized by removing benzamide group or introducing ethyl ester group,respectively (Scheme 2).

The final products were purified by silica gel chromatography. The structures of the compounds were characterized by proton nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR), infrared spectrum (IR) and mass spectrum (MS). Representative ^{1}H and ^{13}C NMR spectra were outlined in Supplement Materials.

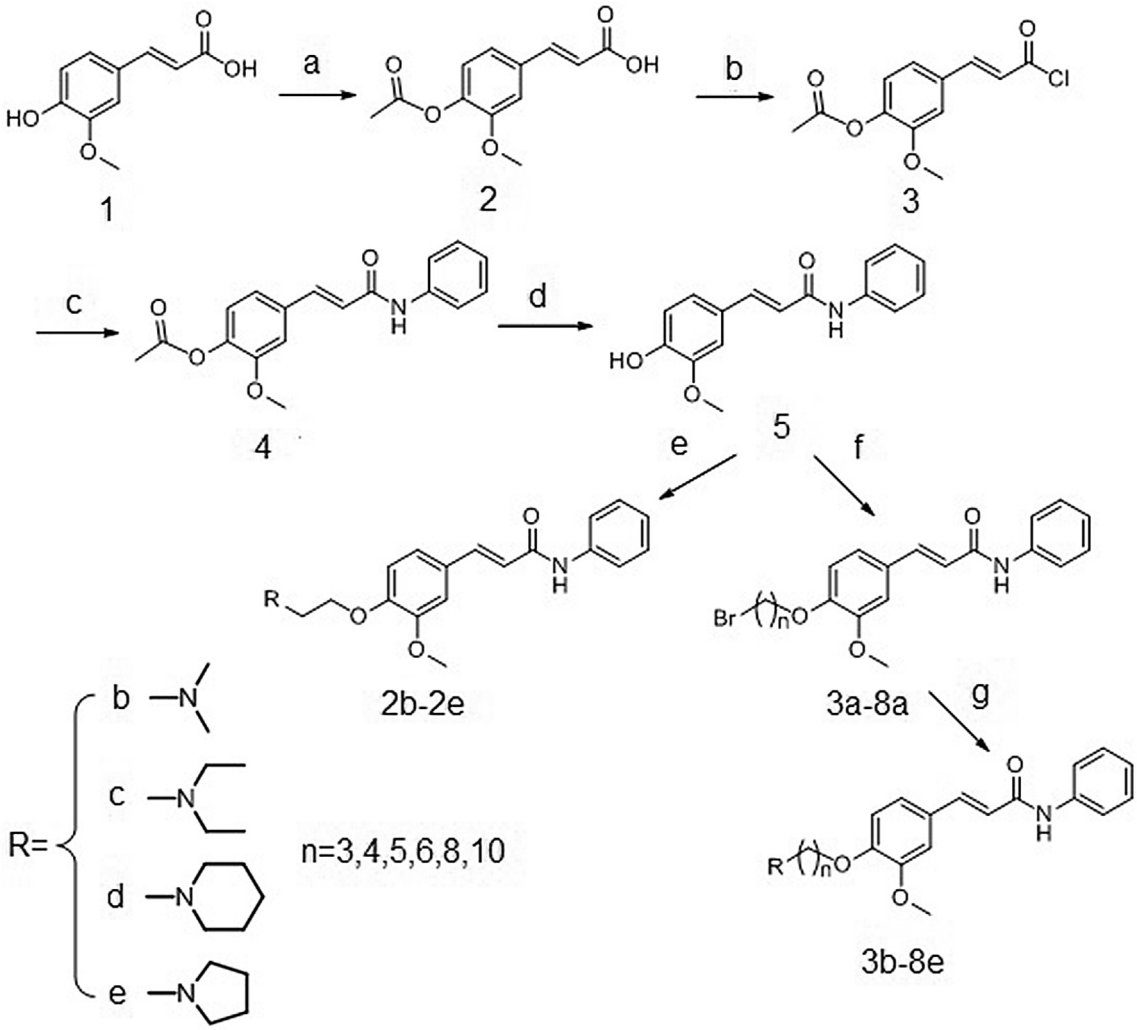
2.2. In vitro inhibition against AChE and BuChE

The half maximal inhibitory concentration (IC_{50} values) of new synthesized compounds in inhibiting AChE and BuChE as well as the selectivity for AChE were shown in Table 1. The results revealed that all of test compounds showed perfect inhibition activity against AChE and BuChE, compared to compound **5** (IC_{50} > 500 μmol/L).

The variation of the spacer linking ferulic acid scaffold and terminal amine groups dramatically influenced the anticholinesterase activity (Table 1). The compounds with six methylenes spacer showed better inhibition activity against AChE (**6b**: 8.40 ± 0.09; **6c**: 1.83 ± 0.22; **6d**: 0.71 ± 0.09; **6e**: 1.11 ± 0.17 μmol/L) than the others. The inhibitory activity against AChE also markedly changed with the alteration of tertiary amine groups. For compounds with the same methylene spacer, most compounds containing piperidine group have more potent inhibition activity against AChE than other derivatives. But for those compounds with eight or ten methylenes spacer, the compounds containing dimethylamine or diethylamine group (compounds **7c** and **8b**) possessed higher activity than the others (Table 1).

Among new synthesized compounds, nine compounds showed better inhibitory activity (IC_{50} = 0.71–8.40 μmol/L) than the control drug Rivastigmine (IC_{50}: 10.54 μmol/L). The most promising compound **6d** (IC_{50}: 0.71 ± 0.09 μmol/L) and **6e** (IC_{50}: 1.11 ± 0.17 μmol/L) possessed 15-fold or 9-fold of inhibitory activity against AChE than that of Rivastigmine, respectively. Moreover, compound **6d** showed the highest selectivity for AChE over BuChE (IC_{50}: 12.97 ± 0.13 μmol/L; ratio: 18.3).

Among new synthesized compounds, compounds **6c, 7c, 6d** and



Scheme 1. Synthesis route of the tertiary derivatives of ferulic acid phenylamine. Reagents and conditions: (a) acetic anhydride, NaOH(aq), HCl(aq), RT; (b) oxalyl chloride, DMF, DCM, 40 °C; (c) aniline, TEA, acetonitrile, 60 °C; (d) ammonium hydroxide, ethanol, RT; (e) $R^1R^2N(CH_2)_2Cl$, K_2CO_3, NaI, acetone, reflux; (f) $Br(CH_2)_nBr$, K_2CO_3, NaI, acetone, reflux; (g) second amine, K_2CO_3, NaI, acetone, reflux.

6e had higher inhibitory activity against AChE. Further study showed that if the benzamide group was removed or replaced by ethyl ester group, the activity in inhibiting AChE decreased significantly. This result suggested that an aromatic group such as benzamide group was possible important for the activity in inhibiting AChE.

In order to study whether the new synthesized compounds had specific inhibitory activity on cholinesterases, the effects of these compounds on carboxylesterase(CaE) was assayed. CaE is thought to detoxicate ester-containing xenobiotics, and the inhibition of CaE could lead to the enhancing toxicity of some exogenous substances [14]. The data showed that all the compounds exhibited high specific inhibition against cholinesterase over CaE (IC_{50} > 500 μmol/L) compared to control drug Rivastigmine (for CaE IC_{50} = 31.1 ± 1.20 μmol/L).

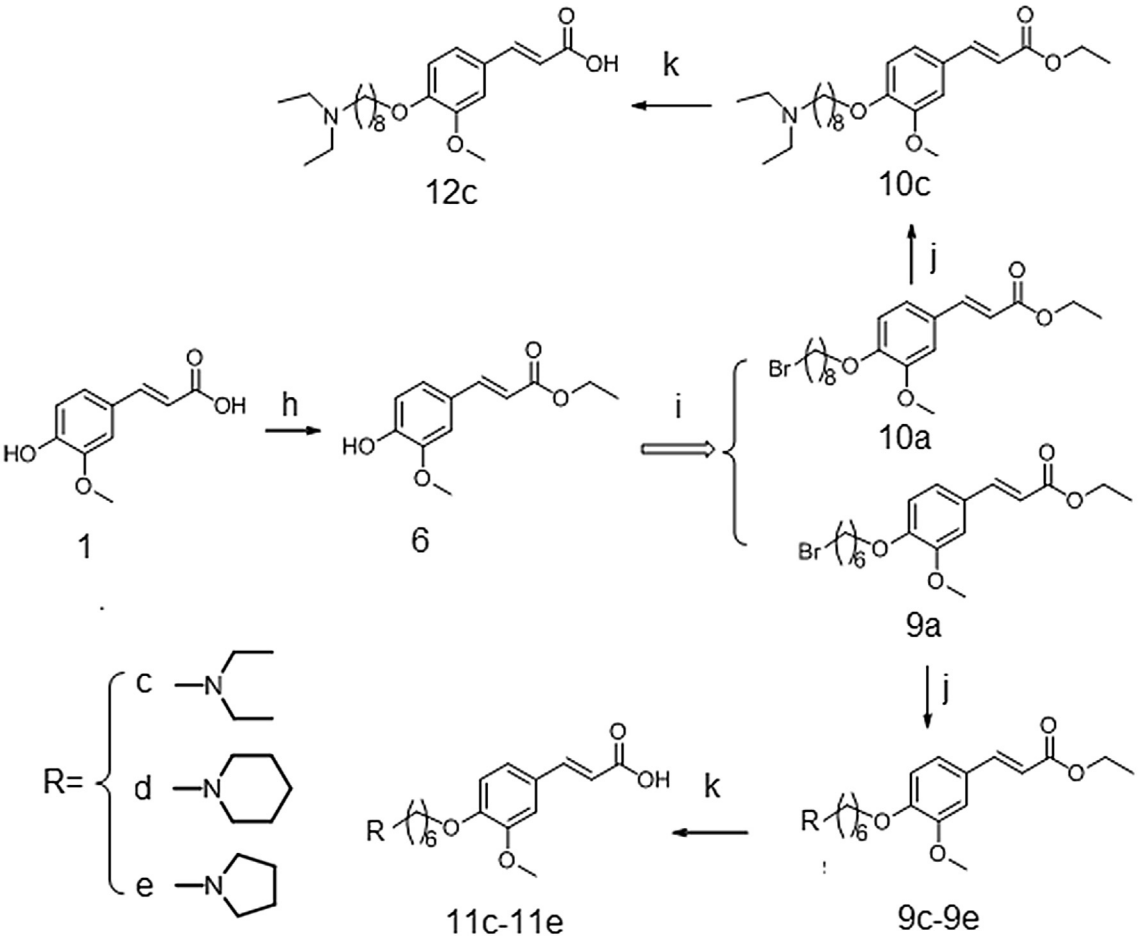
Some previous investigations reported some ferulic acid derivatives incorporated with structure fragment of clinic applied drugs such as Tarcine or Donepezil revealed AChE inhibitory activity, but no detail structure-activity relationship study was carried out further [15–18]. In the present investigation, primary structure-activity relationship about ferulic acid derivatives as AChE inhibitors was elucidated, which was possible beneficial for the development of potent or selective AChE inhibitors for the further.

2.3. LogP measurement

Log P was an important physical chemistry parameter to predict the ability to cross blood brain barrier (BBB), and the optimum logP of compounds for central nervous system (CNS) penetration was around 2 ± 0.7 according to the report [19]. As shown in Table 1, log P values of new synthesized compounds ranged from 1.29 to 1.98, which suggested that most of the compounds possess enough lipophilicify to pass the BBB *in vivo*.

2.4. Kinetic studies

Compound **6d** was selected for kinetic study to evaluate the profile in inhibiting AChE. The linear Lineweaver–Burk equation was applied in this experiment. The graphical analysis of the steady-state inhibition data of compound **6d** was shown in Supplement Fig. 2. According to the analysis, the kinetic profile of compound **6d** revealed a mixed-type inhibition. It suggested that compound **6d** could bind with the catalytic site and the non-



Scheme 2. Synthesis route of the tertiary amine derivatives of ferulic acid and ethyl ferulate. Reagents and conditions: (h) acetylchloride, absolute ethanol, RT; (i) $Br(CH_2)_nBr$, K_2CO_3, NaI, acetone, reflux; (j) second amine, K_2CO_3, NaI, acetone, reflux; (k) 10%NaOH, ethanol, RT.

catalytic site of the AChE with different equilibrium constants, and the competitive constant (Ki) and the non-competitive constant (Ki') are 0.48 and 0.92 μmol/L, respectively (Supplement Table 2).

2.5. Molecular modeling studies

In order to explore possible binding mechanism to AChE and BuChE, a further computational study was performed for compound **6d** using Molecular Operating Environment (MOE). The results from the docking on AChE and BuChE illustrated in Supplement Fig. 3. The results showed that Compound **6d** bind with AChE via multiple sites. The quaternary nitrogen of piperidine ring binds to the catalytic active site (CAS) via the π-cation interaction with Trp84 (4.21 Å), and. the aromatic rings at the top of peripheral anionic site (PAS) interact with Tyr334 (4.26 Å) and Trp279 (4.07 Å) through a π-π stacking effect (Supplement Fig. 3, A). While compound **6d** revealed a weaker affinity in binding to BuChE, only.Gly66 (4.15 Å) and Tyr67 (4.07 Å) combined with BuChE via a π-cation interaction (Supplement Fig. 3, B). Based on these results above, the weak affinity of compound **6d** binding to BuChE may be partially explained the high selectivity in inhibiting AChE.

3. Conclusions

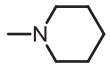
Based on our investigations of chalcone derivatives as AChE inhibitors, a series of novel ferulic acid amide derivatives with tertiary amines side chain were synthesized and evaluated in inhibiting AChE and BuChE. The alteration of carbon chain linking side chain and ferulic acid scaffold as well as the difference of tertiary amine side chain markedly influenced the inhibition activity against AChE. Among them, compound **6d** with IC_{50} value of 0.71 ± 0.09 μmol/L exhibited the best inhibitory effect and the highest selectivity for AChE over BuChE. Further study showed that If the benzamide group in compound **6d** was removed or replaced by ethyl ester group, the inhibitory activity against AChE would decrease by 3.7 or 64 folds, respectively. Enzyme kinetic and molecular docking study revealed that compound **6d** presented a mixed-type inhibition against AChE. It might act as a potential agent for the treatment of AD.

4. Experimental

4.1. Chemistry

^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument using trimethylsilyl (TMS) as the internal standard. Mass spectra were obtained by Finnigan LCQ Advantage MAX with electrospray ionization (ESI-MS) method. Infrared spectrum was obtained by Shimadzu Infinity-1 infrared spectrometer. The purity of compounds was checked by Shimadzu LC-20A high performance liquid chromatography. The melting points were measured by a WRS-lA melting point detector. All chemicals and reagents were of analytical reagent grade and used without further purification.

Table 1
Cholinesterase inhibitory activity and selectivity of synthesized compounds.

Compound	R	n	IC_{50}[a] (μmol/L)			Selective for AChE[b]	logP
			CaE	AChE	BuChE		
5			>500	>500	>500	–	1.42
2b		2	>500	23.20 ± 0.44	23.28 ± 0.44	1.00	1.50
3b		3	>500	33.86 ± 0.55	20.02 ± 0.86	0.59	1.55
4b		4	>500	100.50 ± 1.92	25.90 ± 0.28	0.26	1.57
5b		5	>500	33.02 ± 3.29	12.08 ± 0.26	0.37	1.61
6b		6	>500	8.40 ± 0.09	6.72 ± 0.59	0.80	1.69
7b		8	>500	8.95 ± 0.19	10.41 ± 0.51	1.16	1.74
8b		10	>500	9.93 ± 0.46	20.58 ± 1.04	2.07	1.80
2c		2	>500	41.06 ± 0.08	11.46 ± 0.01	0.28	1.53
3c		3	>500	23.72 ± 2.26	16.88 ± 0.50	0.71	1.57
4c		4	>500	41.63 ± 1.42	25.07 ± 1.78	0.60	1.59
5c		5	>500	18.98 ± 2.74	22.15 ± 0.64	1.17	1.63
6c		6	>500	1.83 ± 0.22	4.86 ± 0.28	2.66	1.70
7c		8	>500	1.36 ± 0.10	3.98 ± 0.26	2.93	1.75
8c		10	>500	14.92 ± 0.83	8.47 ± 0.38	0.57	1.83
9c		6	>500	1.94 ± 0.12	11.38 ± 1.06	5.87	1.80
11c		6	>500	2.67 ± 0.15	263.11 ± 1.88	98.6	1.29
10c		8	>500	1.56 ± 0.27	13.05 ± 1.71	8.37	1.98
12c		8	>500	3.18 ± 0.29	302.45 ± 2.16	95.1	1.51
2d		2	>500	19.40 ± 1.10	2.34 ± 0.15	0.12	1.56
3d		3	>500	14.48 ± 1.82	4.78 ± 0.76	0.33	1.58
4d		4	>500	7.14 ± 0.18	5.69 ± 0.01	0.80	1.61
5d		5	>500	4.80 ± 0.31	5.90 ± 0.67	1.23	1.65
6d		6	>500	0.71 ± 0.08	12.97 ± 0.13	18.3	1.77
7d		8	>500	4.12 ± 0.28	5.45 ± 0.49	1.32	1.79
8d		10	>500	11.11 ± 0.83	4.84 ± 0.64	0.44	1.83
9d		6	>500	2.65 ± 0.33	41.76 ± 1.23	15.8	1.81
11d		6	>500	45.55 ± 1.42	145.69 ± 2.94	3.20	1.32
2e		2	>500	35.13 ± 0.33	12.68 ± 1.12	0.36	1.54
3e		3	>500	37.14 ± 2.84	14.19 ± 0.70	0.38	1.57
4e		4	>500	24.35 ± 1.58	3.83 ± 0.42	0.16	1.60
5e		5	>500	6.21 ± 0.45	4.78 ± 0.35	0.77	1.64
6e		6	>500	1.11 ± 0.17	2.23 ± 0.18	2.01	1.76
7e		8	>500	2.91 ± 0.07	4.03 ± 0.09	1.38	1.78
8e		10	>500	13.52 ± 0.65	2.99 ± 0.07	0.22	1.86
9e		6	>500	5.05 ± 0.35	376.71 ± 1.83	74.6	1.82
11e		6	>500	69.91 ± 4.90	286.72 ± 2.16	4.10	1.29
Rivastigmine[c]	–	–	31.12 ± 1.21	10.54 ± 0.86	0.26 ± 0.08	0.02	1.68

[a] IC_{50}: 50% inhibitory concentration (means ± SD of three experiments).
[b] Selectivity for AChE is defined as IC_{50} (BuChE)/IC_{50} (AChE).
[c] Used for positive control.

4.2. Synthesis of (E)-3-(4-acetoxy-3-methoxyphenyl) acrylic acid (2)

Ferulic acid (**1**) (3.88 g, 20 mmol) was added into 10% NaOH solution (20 mL), then the mixture was place in ice bath, adding acetic anhydride (2.54 g, 25 mmol). The mixture was stirred keeping at 20 °C for 10 min and placed at room temperature for 20 min. Then the pH value was adjusted to 4–5 by adding dilute hydrochloric acid. The mixture was filtered and the precipitate was gained after washing by water. Finally compound **2** (colorless needles crystal, 3.12 g, yield 66%) was gained by re-crystallization from ethanol.

4.3. (E)-4-(3-chloro-3-oxoprop-1-en-1-yl)-2-methoxyphenyl acetate (3)

Oxalyl chloride (2.55 mL, 30 mmol) was added to a suspension of compound **2** (2.36 g, 10 mmol) in CH_2Cl_2 (40 mL) containing a catalytic amount of dimethylformamide (DMF). The mixture was refluxed and stirred for 6 h. After the solvent and excess oxalyl chloride was removed under reduced pressure, pale yellow crystals were obtained. This material was used directly for the next reaction without further purification.

4.4. (E)-2-methoxy-4-(3-oxo-3-(phenylamino)prop-1-en-1-yl) phenyl acetate(4)

Phenylamine (1 mL, 11 mmol) was dropped slowly to a solution of compound **3** (2.5 g, 10 mmol) in acetonitrile (20 mL) in ice bath. The mixture was stirred for 8 h at room temperature until the reaction was completed. After the solvent was removed under reduced pressure, the light yellow viscous liquid was obtained, and this material was used for the next reaction without further purification.

4.5. (E)-3-(4-hydroxy-3-methoxyphenyl)-N-phenylacrylamide(5)

Compound **4** was hydrolyzed by ammonium hydroxide. After the solvent was removed under reduced pressure, the crude product was added into 20% sodium hydroxide solution. The solution was cooled to 5–6°C and then filtered. A solution containing 10% hydrochloric acid was slowly added to the filtrate, adjusting the pH of solution to 3–4, and the yellow precipitate produced with a yield of 55%, which was proved as the intermediate compound **5**.

4.6. General procedure for the synthesis of 2b–2e

The mixture containing compound **5** (1.5 mmol), K_2CO_3 (1.055 g,

7.5 mmol) and NaI (0.012 g, 0.05 mmol) in acetone (20 mL) was stirred for 30 min at 56°C, then aminoethyl chloride (4.5 mmol) were added into the mixture and kept refluxing for 10 h until the reaction was completed. Then the reaction mixture was cooled to room temperature and filtered. The filtrate was concentrated under reduced pressure and partitioned between brine and CH_2Cl_2. The separated organic phase was washed by 10% NaOH, dried with anhydrous Na_2SO_4. After the solvent was removed in vacuum, the crude product was gained and purified by silica-gel column chromatography with methanol/dichloromethane as eluting solution. Compound **2b-2e** was gained with the yield of 45–60%, respectively.

4.6.1. (E)-3-(4-(2-(dimethylamino)ethoxy)-3-methoxyphenyl)-N-phenylacrylamide (2b)

Light yellow viscous liquid, yield: 46.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 2.22 (6H, s, 2 × NC$\underline{H}_3$), 2.62–2.65 (2H, t, J = 12.0 Hz, OCH$_2$C$\underline{H}_2$), 3.83 (3H, s, OC$\underline{H}_3$), 4.07–4.10 (2H, t, J = 12.0 Hz, OC$\underline{H}_2$CH$_2$), 6.69–6.73 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.03–7.07 (2H, m, Ar-$\underline{H}$), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.22 (1H, s, Ar-$\underline{H}$), 7.31–7.35 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.51–7.55 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-$\underline{H}$), 10.14 (1H, s, N$\underline{H}$). ^{13}CNMR (400 MHz, CDCl$_3$) δ (ppm): 27.3, 45.5(2), 56.2, 67.3, 110.4, 112.4, 112.7, 122.2(2), 127.6, 129.1(2), 138.2, 142.3, 146.7, 149.7(2), 150.4, 164.4. IR (KBr) m/cm^{-1}: 3373, 1654, 1549, 1516, 1489, 1442, 1261, 1184. MS m/z (ESI): 341 [M+H]$^+$. Purity: 98.3% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.6.2. (E)-3-(4-(2-(diethylamino)ethoxy)-3-methoxyphenyl)-N-phenylacrylamide (2c)

Yellow viscous liquid, yield: 56.3%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.96–0.99 (6H, t, J = 12.0 Hz, 2 × NCH$_2$C$\underline{H}_3$), 2.52–2.58 (4H, m, 2 × NC$\underline{H}_2$CH$_3$), 2.77–2.80 (2H, t, J = 12.0 Hz, OCH$_2$C$\underline{H}_2$), 3.82 (3H, s, OC$\underline{H}_3$), 4.02–4.06 (2H, t, J = 12.0 Hz, OC$\underline{H}_2$CH$_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.02–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.21 (1H, s, Ar-$\underline{H}$), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.68–7.70 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, CDCl$_3$) δ (ppm): 11.7(2), 47.7(2), 51.6, 55.9, 67.2, 110.3, 112.4(2), 119.9, 122.1, 124.3, 127.7, 129.1(2), 138.3, 142.2, 149.3(2), 150.1, 164.4. IR (KBr) m/cm^{-1}: 3376, 1647, 1598, 1541, 1490, 1442, 1259, 1182. MS m/z (ESI): 369 [M+H]$^+$. Purity: 97.9% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.6.3. (E)-3-(3-methoxy-4-(2-(piperidin-1-yl)ethoxy)phenyl)-N-phenylacrylamide (2d)

Yellow viscous liquid, yield: 47.9%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.48–1.49 (4H, m, piperidine-H), 1.56 (2H, m, piperidine-H), 2.42 (4H, m, piperidine-H), 2.68–2.71 (2H, t, J = 12.0 Hz, OCH$_2$C$\underline{H}_2$), 3.84 (3H, s, OC$\underline{H}_3$), 3.91 (2H, t, J = 12.0 Hz, OC$\underline{H}_2$CH$_2$), 6.75–6.79 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.04–7.11 (2H, m, Ar-H), 7.22–7.24 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.28 (1H, s, Ar-$\underline{H}$), 7.31–7.35 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.52–7.56 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.18 (1H, s, NH). ^{13}C NMR (400 MHz, CDCl$_3$) δ (ppm): 20.2, 25.8(2), 53.5(2), 54.7, 55.7, 60.3, 100.0, 109.4, 114.4(2), 119.9, 128.8, 129.3(2), 130.2, 139.4, 147.6, 148.2(2), 149.5, 164.6.IR (KBr) m/cm^{-1}: 3421, 1652, 1585, 1539, 1498, 1456, 1195, 1195. MS m/z (ESI): 381 [M+H]$^+$. Purity: 98.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.6.4. (E)-3-(3-methoxy-4-(2-(pyrrolidin-1-yl)ethoxy)phenyl)-N-phenylacrylamide (2e)

Yellow viscous liquid, yield: 59.2%. ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.69 (4H, m, pyrrolidine-H), 1.87–1.94 (2H, m, OCH$_2$C$\underline{H}_2$), 2.50 (4H, m, pyrrolidine-H), 3.82 (3H, s, OC$\underline{H}_3$), 4.02–4.06 (2H, t, J = 12.0 Hz, OC$\underline{H}_2$CH$_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.02–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.21 (1H, s, Ar-$\underline{H}$), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.68–7.70 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, CDCl$_3$) δ (ppm): 11.69(2), 47.7, 51.6(2), 55.9, 67.2, 110.3, 112.4(2), 119.9, 122.1, 124.3, 127.7, 129.1(2), 138.3, 142.2, 149.3(2), 150.1, 164.4. IR (KBr) m/cm^{-1}: 3435, 1663, 1595, 1541, 1490, 1436, 1259, 1161. MS m/z (ESI): 367 [M+H]$^+$. Purity: 98.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.7. General procedure for the synthesis of intermediate 3a–8a

A mixture of compound **5** (1.353 g, 5 mmol) with an appropriate of α,ω-dibromoalkanes (15 mmol) and anhydrous K_2CO_3 (3.4371 g, 25 mmol) in acetone was refluxed and stirred for 4–10 h until the reaction was completed with TLC examination. After cooling, the reaction mixture was filtered and the solvent was evaporated under reduced pressure, then the residue was partitioned between H_2O and CH_2Cl_2. The separated organic layer was washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solvent was concentrated in vacuum and the residue was purified by silica gel chromatography with ethyl acetate/petroleum ether (15:1, v/v) as eluant to achieve product **3a-8a**, and the yield ranged 70%–85%.

4.7.1. (E)-3-(4-(3-bromopropoxy)-3-methoxyphenyl)-N-phenylacrylamide (3a)

White solid, yield:76.4%, mp: 154.6–155.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.84–1.88 (2H, m, OCH$_2$C$\underline{H}_2$CH$_2$), 2.33–2.37 (2H, t, J = 16.0 Hz, OCH$_2$CH$_2$C$\underline{H}_2$), 3.83 (3H, s, OC$\underline{H}_3$), 4.01–4.05 (2H, t, J = 16.0 Hz, OC$\underline{H}_2$CH$_2$CH$_2$), 6.69–6.73 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.00–7.06 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.22 (1H, s, Ar-$\underline{H}$), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.69–7.71 (2H, d, J = 8.0 Hz, Ar-H), 10.13 (1H, s, NH). MS m/z (ESI): 391 [M+H]+. Purity: 97.6% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.7.2. (E)-3-(4-(4-bromobutoxy)-3-methoxyphenyl)-N-phenylacrylamide (4a)

White solid, yield:79.3%, mp: 149.1–150.7°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.67–1.69 (2H, m, OCH$_2$CH$_2$C$\underline{H}_2$CH$_2$), 1.74–1.75 (2H, m, OCH$_2$C$\underline{H}_2$CH$_2$CH$_2$), 2.70 (2H, t, J = 16.0 Hz, OCH$_2$CH$_2$CH$_2$C$\underline{H}_2$), 3.83 (3H, s, OC$\underline{H}_3$), 4.01–4.04 (2H, t, J = 16.0 Hz, OC$\underline{H}_2$CH$_2$CH$_2$CH$_2$), 6.71–6.75 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.01–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.22 (1H, s, Ar-$\underline{H}$), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-$\underline{H}$), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.69–7.71 (2H, d, J = 8.0 Hz, Ar-H), 10.14 (1H, s, NH). MS m/z (ESI): 405 [M+H]+. Purity: 98.3% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.7.3. (E)-3-(4-((5-bromopentyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (5a)

White solid, yield:80.3%, mp: 144.6–145.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.49–1.56 (4H, m, OCH$_2$CH$_2$C$\underline{H}_2$C$\underline{H}_2$CH$_2$), 1.79–1.86 (2H, m, OCH$_2$C$\underline{H}_2$CH$_2$CH$_2$CH$_2$), 2.29–2.32 (2H, t, J = 12.0 Hz, OCH$_2$CH$_2$CH$_2$CH$_2$C$\underline{H}_2$), 3.91 (3H, s, OC$\underline{H}_3$), 4.07–4.10 (2H, t, J = 12.0 Hz, OC$\underline{H}_2$CH$_2$CH$_2$CH$_2$CH$_2$), 6.77–6.81 (1H, d, J = 16.0 Hz, Ar-CH=C$\underline{H}$), 7.09–7.16 (2H, m, Ar-H), 7.24–7.26 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.30 (1H, s, Ar-$\underline{H}$), 7.39–7.43 (2H, J = 16.0 Hz, Ar-$\underline{H}$), 7.59–7.63 (1H, d, J = 16.0 Hz, Ar-C$\underline{H}$=CH), 7.77–7.79 (2H, d, J = 8.0 Hz, Ar-H), 10.19 (1H, s, NH). MS m/z (ESI): 419 [M+H]+. Purity: 96.9% by HPLC MeOH/0.1% TEA 85:15 (v/v).

4.7.4. (E)-3-(4-((6-bromohexyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (6a)

White solid, yield: 85.3%, mp: 133.5–134.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.32–1.36 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.41–1.44 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.69–1.76 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.23–2.26 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.69–6.72 (1H, d, J = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, J = 8.0 Hz, Ar-H), 10.11 (1H, s, NH). MS m/z (ESI): 433 [M+H]+. Purity: 97.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.7.5. (E)-3-(4-((8-bromooctyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (7a)

White solid, yield: 82.8%, mp: 126.8–128.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28–1.48 (10H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 1.70–1.74 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 2.33 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 3.97–4.01 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). MS m/z (ESI): 461 [M+H]+. Purity: 97.9% by HPLC MeOH/0.1% TEA 85:15 (v/v).

4.7.6. (E)-3-(4-((10-bromodecyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (8a)

White solid, yield: 83.5%, mp: 115.3–116.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24–1.50 (16H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 1.70–1.73 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.68–7.70 (2H, d, J = 8.0 Hz, Ar-H), 10.10 (1H, s, NH). MS m/z (ESI): 489 [M+H]+. Purity: 98.2% by HPLC MeOH/0.1% TEA 85:15 (v/v).

4.8. General procedure for the synthesis of 3b-8e

A mixture of compound **3a** (1 mmol) with secondary amines (dimethylamine, diethylamine, piperidine, pyrrolidine), anhydrous K_2CO_3 (0.6822 g, 7.5 mmol), NaI (0.011 g, 0.05 mmol) in acetone (20 mL) was refluxed and stirred for 8 h. After cooling to the room temperature, the reaction mixture was filtered. The filtrate was evaporated in vacuum and the residue was dissolved with CH_2Cl_2 (30 mL). Then the organic phase was washed by saturated NaCl solution (2 × 20 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuum. The residue was purified by silica gel chromatography with different ratio of CH_2Cl_2/MeOH as eluant to achieve target compound **3b**. The other compounds were synthesized by similar method as mentioned above.

4.8.1. (E)-3-(4-(3-(dimethylamino)propoxy)-3-methoxyphenyl)-N-phenylacrylamide (3b)

White solid, yield: 78.2%, mp: 99.7–101.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.84–1.88 (2H, m, $OCH_2CH_2CH_2$), 2.14 (6H, s, 2 × NCH_3), 2.33–2.37 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 4.01–4.05 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2$), 6.69–6.73 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.00–7.06 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.13 (1H, s, NH). ^{13}CNMR (400 MHz, $CDCl_3$) δ (ppm): 27.3, 45.5(2), 56.0, 56.2, 67.3, 110.4, 112.4, 112.7, 122.2(2), 127.6, 129.1(2), 138.2, 142.3, 146.7, 149.7(2), 150.4, 164.2.IR (KBr) m/cm^{-1}: 3411, 1656, 1597, 1581, 1498, 1442, 1288, 1180. MS m/z (ESI): 355 [M+H]$^+$. Purity: 97.2% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.2. (E)-3-(4-(3-(diethylamino)propoxy)-3-methoxyphenyl)-N-phenylacrylamide(3c)

White solid, yield: 78.5%, mp:104.8–106.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.93–0.97 (6H, t, J = 16.0 Hz, 2 × NCH_2CH_3), 1.81–1.84 (2H, m, $OCH_2CH_2CH_2$), 2.46–2.50 (6H, m, 3 × NCH_2), 3.82 (3H, s, OCH_3), 4.02–4.05 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$)δ (ppm): 11.7(2), 26.6, 46.9(2), 49.7, 55.9, 67.5, 110.4, 112.7, 119.9, 122.2(2), 124.3, 127.6, 129.1(2), 138.3, 142.3, 149.5(2), 150.4, 164.3.IR (KBr) m/cm^{-1}:3446, 1660, 1581, 1541, 1490, 1438, 1296, 1199. MS m/z (ESI): 383 [M+H]$^+$. Purity: 98.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.3. (E)-3-(3-methoxy-4-(3-(piperidin-1-yl)propoxy)phenyl)-N-phenylacrylamide(3d)

Light yellow solid, yield: 72.2%, mp: 81.8–83.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.38 (2H, m, piperidine-H), 1.50 (4H, m, piperidine-H), 1.88 (2H, m, $OCH_2CH_2CH_2$), 2.34 (6H, m, 3 × NCH_2), 3.82 (3H, s, OCH_3), 4.02–4.05 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.01–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.68–7.70 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, CDC_{l3}) δ (ppm): 11.7(2), 26.6, 46.9, 49.2(2), 55.9, 61.0, 67.5, 110.4, 112.7, 119.2, 122.2(2), 124.3, 127.6, 129.1(2), 138.3, 142.9, 149.5(2), 150.4, 164.3.IR (KBr) m/cm^{-1}: 3441, 1662, 1597, 1583, 1489, 1442, 1178, 1165. MS m/z (ESI): 395 [M+H]+. Purity: 97.3% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.4. (E)-3-(3-methoxy-4-(3-(pyrrolidin-1-yl)propoxy)phenyl)-N-phenylacrylamide(3e)

Light yellow solid, yield: 75.8%, mp: 91.7–93.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.69 (4H, m, pyrrolidine-H), 1.87–1.94 (2H, m, $OCH_2CH_2CH_2$), 2.50 (4H, m, pyrrolidine-H), 2.55–2.58 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.03–4.06 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2$), 6.69–6.73 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, CDC_{l3}) δ (ppm): 11.7(2), 26.6, 46.9, 49.2(2), 55.9, 67.5, 110.4, 112.7, 119.2, 122.2(2), 124.3, 127.6, 129.1(2), 138.3, 142.9, 149.5(2), 150.4, 164.3. IR (KBr) m/cm^{-1}: 3649, 1627, 1500, 1544, 1465, 1421, 1184, 1165. MS m/z (ESI): 381 [M+H]+. Purity: 98.0% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.5. (E)-3-(4-(4-(dimethylamino)butoxy)-3-methoxyphenyl)-N-phenylacrylamide(4b)

Light yellow solid, yield: 81.2%, mp: 90.2–92.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.67–1.69 (2H, m, $OCH_2CH_2CH_2CH_2$), 1.74–1.75 (2H, m, $OCH_2CH_2CH_2CH_2$), 2.45 (6H, s, 2 × NCH_3), 2.70 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 4.01–4.04 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2$), 6.71–6.75 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.01–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.30–7.34 (2H, t, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.14

(1H, s, NH). ^{13}CNMR (400 MHz, $CDCl_3$) δ (ppm): 27.3, 45.5(2), 56.0, 56.2, 66.8, 67.3, 110.4, 112.4, 112.7, 122.2(2), 127.6, 129.1(2), 138.2, 142.3, 146.7, 149.7(2), 150.4, 164.2. IR (KBr) m/cm^{-1}: 3460, 1600, 1595, 1544, 1490, 1469, 1184, 1165. MS *m/z* (ESI): 369 [M+H]+. Purity: 98.5% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.6. (E)-3-(4-(4-(diethylamino)butoxy)-3-methoxyphenyl)-N-phenylacrylamide(4c)

Yellow solid, yield: 83.4%, mp: 94.0–95.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 0.93–0.96 (6H, t, *J* = 12.0 Hz, 2 × CH_3), 1.50–1.56 (2H, m, $OCH_2CH_2CH_2CH_2$), 1.69–1.76 (2H, m, $OCH_2CH_2CH_2CH_2$), 2.44–2.46 (6H, m, 3 × NCH_2 and $OCH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, *J* = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, *J* = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.68–7.70 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$)δ (ppm): 23.9(2), 27.3, 29.0, 45.4(2), 55.9, 59.5, 68.6, 100.0, 110.3, 112.4(2), 119.9, 122.2, 127.5, 129.1(2), 138.3, 142.2, 149.4(2), 150.4, 164.5.IR (KBr) m/cm^{-1}: 3433, 1670, 1595, 1556, 1519, 1469, 1184, 1099. MS *m/z* (ESI): 369 [M+H]+. Purity: 98.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.7. (E)-3-(3-methoxy-4-(4-(piperidin-1-yl)butoxy)phenyl)-N-phenylacrylamide(4d)

Light yellow solid, yield: 85.1%, mp: 92.3–94.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (2H, m, $OCH_2CH_2CH_2CH_2$), 1.40 (2H, m, piperidine-H), 1.52 (4H, m, piperidine-H), 1.60 (2H, m, $OCH_2CH_2CH_2CH_2$), 1.70–1.75 (2H, m, $OCH_2CH_2CH_2CH_2$), 2.42 (4H, m, piperidine-H), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2$), 6.69–6.74 (1H, dd, *J* = 4.0 Hz, *J* = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, *J* = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, *J* = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.14 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.5, 23.4(2), 27.1, 29.7, 46.7(2), 52.5, 56.9, 68.8, 110.3, 112.5, 119.9, 122.2(2), 124.3, 127.6, 129.1(2), 138.3, 142.2, 149.5(2), 150.1, 164.4. IR (KBr) m/cm^{-1}: 3394, 1647, 1597, 1541, 1490, 1467, 1182, 1078. MS *m/z* (ESI): 409 [M+H]+. Purity: 96.4% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.8. (E)-3-(3-methoxy-4-(4-(pyrrolidin-1-yl)butoxy)phenyl)-N-phenylacrylamide(4e)

Light yellow solid, yield: 85.0%, mp: 93.7–95.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.23 (2H, m, $OCH_2CH_2CH_2CH_2$), 1.69 (4H, m, pyrrolidine-H), 1.76 (2H, m, $OCH_2CH_2CH_2CH_2$), 2.50 (4H, m, pyrrolidine-H), 2.55–2.58 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2$), 6.69–6.74 (1H, dd, *J* = 4.0 Hz, *J* = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, *J* = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, *J* = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.14 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 23.8(2), 27.2, 28.9, 45.3(2), 55.9, 59.5, 68.6, 99.9, 110.3, 112.4(2), 119.9, 122.2, 127.5, 129.1(2), 138.3, 142.2, 149.2(2), 150.3, 164.5. IR (KBr) m/cm^{-1}: 3315, 1670, 1581, 1558, 1487, 1463, 1188, 1091. MS *m/z* (ESI): 395 [M+H]+. Purity: 98.5% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.9. (E)-3-(4-((5-(dimethylamino)pentyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide(5b)

White solid, yield: 83.0%, mp: 94.7–95.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.49–1.56 (4H, m, $OCH_2CH_2CH_2CH_2CH_2$), 1.79–1.86 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.21 (6H, s, 2 × NCH_3), 2.29–2.32 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 3.91 (3H, s, OCH_3), 4.07–4.10 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 6.77–6.81 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.09–7.16 (2H, m, Ar-H), 7.24–7.26 (1H, d, *J* = 8.0 Hz, Ar-H), 7.30 (1H, s, Ar-H), 7.39–7.43 (2H, *J* = 16.0 Hz, Ar-H), 7.59–7.63 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.77–7.79 (2H, d, 8.0 Hz, Ar-H), 10.19 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 23.9, 27.3, 29.0, 45.4(2), 55.9, 59.5, 68.6, 100.0, 110.3, 112.4(2), 119.9, 122.2, 127.5, 129.1(2), 138.3, 142.2, 149.4(2), 150.4, 164.5.IR (KBr) m/cm^{-1}: 3298, 1668, 1627, 1600, 1556, 1489, 1188, 1097. MS *m/z* (ESI): 383 [M+H]$^+$. Purity: 98.7% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.10. (E)-3-(4-((5-(diethylamino)pentyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide(5c)

White solid, yield: 85.1%, mp: 93.8–95.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.06–1.09 (6H, t, *J* = 12.0 Hz, 2 × NCH_2CH_3), 1.42–1.48 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 1.84–1.87 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 1.73–1.80 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.81 (6H, t, *J* = 12.0 Hz, 3 × NCH_2), 3.83 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 6.70–6.74 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.01–7.08 (2H, m, Ar-H), 7.16–7.18 (1H, d, *J* = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31–7.35 (2H, *J* = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.13 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 10.25(1), 23.9, 25.2, 28.8, 46.7(2), 52.2, 55.9, 68.7, 99.9, 110.4, 112.6, 122.1(2), 124.2, 127.7(2), 129.0, 138.3, 149.4(2), 150.2, 154.2, 164.3. IR (KBr) m/cm^{-1}: 3399, 1668, 1600, 1581, 1544, 1456, 1165, 1066. MS *m/z* (ESI): 411 [M+H]$^+$. Purity: 97.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.11. (E)-3-(3-methoxy-4-((5-(piperidin-1-yl)pentyl)oxy)phenyl)-N-phenylacrylamide(5d)

Light yellow solid, yield: 76.1%, mp: 190.9–192.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.42–1.47 (4H, m, $OCH_2CH_2CH_2CH_2CH_2$), 1.64 (6H, m, piperidine-H), 1.73–1.78 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.67–2.73 (6H, m, 3 × NCH_2), 3.83 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 6.70–6.74 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.01–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, *J* = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31–7.34 (2H, *J* = 12.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 10.2(2), 23.8, 25.2, 28.7, 46.7(2), 52.2, 53.5, 55.9, 68.7, 110.5, 112.5, 119.9, 122.0(2), 124.1, 127.8, 128.9(2), 138.5, 141.8, 149.3(2), 150.1, 164.6. IR (KBr) m/cm^{-1}: 3298, 1668, 1627, 1600, 1556, 1489, 1188, 1097. MS *m/z* (ESI): 423 [M+H]$^+$. Purity: 97.9% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.12. (E)-3-(3-methoxy-4-((5-(pyrrolidin-1-yl)pentyl)oxy)phenyl)-N-phenylacrylamide(5e)

Light yellow solid, yield: 70.5%, mp: 198.9–200.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.42–1.47 (4H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.68 (4H, m, pyrrolidine-H), 1.73–1.78 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.54 (4H, m, pyrrolidine-H), 2.55–2.58 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2$ CH_2CH_2), 3.83 (3H, s, OCH_3), 4.00–4.03 (2H, t, *J* = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 6.70–6.74 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.01–7.07 (2H, m, Ar-H), 7.16–7.18 (1H, d, *J* = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31–7.34 (2H, *J* = 12.0 Hz, Ar-H), 7.50–7.54 (1H, d, *J* = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH).

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 10.2(2), 23.8, 28.7, 46.7(2), 52.2, 53.5, 55.9, 68.7, 110.5, 112.5, 119.9, 122.0(2), 124.1, 127.8, 128.9(2), 138.5, 141.8, 149.3(2), 150.1, 164.6.IR (KBr) m/cm^{-1}: 3346, 1687, 1598, 1581, 1541, 1498, 1172, 1078. MS *m/z* (ESI): 410 [M+H]$^+$. Purity: 95.5% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.13. (E)-3-(4-((6-(dimethylamino)hexyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide(6b)

White solid, yield: 78.1%, mp: 110.9–112.3°C; ^{1}H NMR

(400 MHz, DMSO-d_6) δ (ppm): 1.32–1.36 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.41–1.44 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.69–1.76 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.15 (6H, s, 2 × NCH_3), 2.23–2.26 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2$), 6.69–6.72 (1H, d, J = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 25.9, 27.2, 27.5, 29.0, 45.4(2), 56.0, 59.7, 68.9, 110.3, 112.5, 118.5, 119.8, 122.3(2), 127.5, 129.1(2), 138.2, 142.4(2), 149.5, 150.5, 157.7. IR (KBr) m/cm^{-1}: 3396, 1672, 1583, 1558, 1514, 1490, 1188, 1080. MS m/z (ESI): 433 $[M+H]^+$. Purity: 96.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.14. (E)-3-(4-((6-(diethylamino)hexyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide(6c)

Light yellow solid, yield: 78.1%, mp: 147.7–149.3°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.06–1.09 (6H, t, J = 12.0 Hz, 2 × NCH_2CH_3), 1.32–1.36 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.41–1.44 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.69–1.76 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.81 (6H, t, J = 12.0 Hz, 3 × NCH_2), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.69–6.72 (1H, d, J = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 10.9(2), 25.0, 25.7, 26.9, 28.9, 46.8(2), 52.1, 56.0, 68.7, 110.4, 112.5(2), 119.9, 122.1, 124.1, 127.8(2), 129.0, 138.6, 141.7, 149.4(2), 150.2, 164.7. IR (KBr) m/cm^{-1}: 3340, 1674, 1598, 1560, 1516, 1492, 1166, 1095. MS m/z (ESI): 425 $[M+H]^+$. Purity: 97.3% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.15. (E)-3-(3-methoxy-4-((6-(piperidin-1-yl)hexyl)oxy)phenyl)-N-phenylacrylamide(6d)

White solid, yield: 71.8%, mp: 103.2–104.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.37–1.48 (12H, m, piperidine-H and $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.70–1.73 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.19–2.23 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.29 (4H, m, piperidine-H), 3.82 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 24.4, 25.9(2), 25.9, 26.7, 27.5, 29.0, 54.6(2), 56.0, 59.5, 68.9, 110.3, 112.4(2), 119.9, 122.2, 124.3, 127.5, 129.1(2), 138.3, 142.3, 149.4(2), 150.5, 164.4. IR (KBr) m/cm^{-1}: 3377, 1674, 1598, 1543, 1516, 1492, 1184, 1095. MS m/z (ESI): 437 $[M+H]^+$. Purity: 98.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.16. (E)-3-(3-methoxy-4-((6-(pyrrolidin-1-yl)hexyl)oxy) phenyl)-N-phenylacrylamide(6e)

White solid, yield: 70.6%, mp: 120.2–121.9°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.42–1.47 (6H, m, $OCH_2CH_2CH_2CH_2CH_2$ CH_2), 2.68 (4H, m, pyrrolidine-H), 1.73–1.78 (2H, m, $OCH_2CH_2CH_2CH_2$ CH_2CH_2), 2.54 (4H, m, pyrrolidine-H), 2.55–2.58 (2H, t, J = 12.0 Hz, OCH_2CH_2 CH_2CH_2 CH_2CH_2), 3.82 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 10.8(2), 25.0, 25.7, 26.9, 28.9, 46.8(2), 52.1, 56.0, 68.7, 110.4, 112.5(2), 119.9, 122.1, 124.1, 127.8(2), 129.0, 138.6, 141.7, 149.4(2), 150.2, 164.7.IR (KBr) m/cm^{-1}: 3340, 1672, 1602, 1558, 1541, 1398, 1166, 1031. MS m/z (ESI): 423 $[M+H]^+$. Purity: 96.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.17. (E)-3-(4-((8-(dimethylamino)octyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (7b)

Light yellow solid, yield: 65.9%, mp: 89.1–90.6°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28–1.48 (10H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 1.70–1.74 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2), 2.15 (6H, s, 2 × NCH_3), 2.23–2.26 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 4.00–4.03 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.69–6.72 (1H, d, J = 12.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.11 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 25.8, 26.4, 27.2, 28.9, 29.2, 29.3(2), 44.5(2), 51.5, 56.0, 59.2, 68.9, 110.4, 112.5, 119.9, 122.2(2), 124.2, 127.6(2), 129.0, 138.4, 142.0, 149.5(2), 150.4, 164.4. IR (KBr) m/cm^{-1}: 3387, 1664, 1600, 1583, 1544, 1467, 1182, 1080. MS m/z (ESI): 425 $[M+H]^+$. Purity: 97.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.18. (E) -3-(4-((8-(diethylamino)octyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (7c)

Light yellow solid, yield: 63.8%, mp: 95.3–96.5°C; ^{1}H NMR (400 MHz, DMSO-$d_6\delta$ (ppm): 1.06–1.09 (6H, t, J = 12.0 Hz, 2 × NCH_2CH_3), 1.28–1.48 (10H, m, $OCH_2CH_2CH_2CH_2$ $CH_2CH_2CH_2CH_2$), 1.70–1.74 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$ $CH_2CH_2CH_2$), 2.33 (6H, m, 3 × NCH_2), 3.82 (3H, s, OCH_3), 3.97–4.01 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.70–6.74 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.01–7.08 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31–7.35 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.13 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.3(2), 25.9, 26.5, 27.7, 29.0, 29.3, 29.4, 29.5, 29.6, 46.8(2), 52.0, 55.9, 69.0, 110.3, 112.4, 119.9, 122.2(2), 124.2, 127.5(2), 129.0, 138.3, 142.2, 149.4(2), 150.4, 164.5. IR (KBr) m/cm^{-1}: 3394, 1678, 1602, 1583, 1552, 1498, 1161, 1080. MS m/z (ESI): 453 $[M+H]^+$. Purity: 98.2% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.19. (E) -3-(4-((8-(piperidin-1-yl)octyl)oxy)3-methoxyphenyl)-N-phenylacrylamide (7d)

Light yellow solid, yield: 78.1%, mp: 113.4–115.1°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28–1.48 (20H, m, piperidine-H and $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2$ CH_2), 1.70–1.74 (2H, m, OCH_2CH_2 $CH_2CH_2CH_2CH_2$ CH_2 CH_2), 2.33 (6H, m, 3 × NCH_2), 3.82 (3H, s, OCH_3), 3.97–4.01 (2H, t, J = 16.0 Hz, OCH_2CH_2 $CH_2CH_2CH_2CH_2$ CH_2 CH_2), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.00–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.68–7.70 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 24.2, 25.5(2), 25.9, 26.5, 27.6, 28.9, 29.3, 29.4, 29.5, 53.5, 54.5(2), 56.0, 59.4, 69.0, 110.3, 112.4, 119.9, 122.3(2), 124.3, 127.4(2), 129.1, 138.3, 142.3, 149.5(2), 150.5, 165.0.IR (KBr) m/cm^{-1}: 3412, 1666, 1598, 1556, 1512, 1498, 1184, 1095. MS m/z (ESI): 465 $[M+H]^+$. Purity: 98.9% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.20. (E) -3-(3-methoxy-4-((8-(pyrrolidin-1-yl)octyl)oxy) phenyl)-N-phenylacrylamide(7e)

Light yellow solid, yield: 78.1%, mp: 101.6–102.7°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.28–1.48 (14H, m, pyrrolidine-H and $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2$ CH_2), 1.70–1.74 (2H, m, OCH_2CH_2 $CH_2CH_2CH_2CH_2$ CH_2CH_2), 2.33 (6H, m, 3 × NCH_2), 3.82

(3H, s, OCH_3), 3.97–4.01 (2H, t, J = 16.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.3(2), 25.9, 26.6, 27.7, 29.0, 29.3, 29.4, 29.5, 29.6, 16.8(2), 52.8, 55.9, 69.0, 110.3, 112.4, 119.8, 122.2(2), 124.2127.5(2), 129.1, 138.3, 142.2, 149.4, 150.1, 165.9. IR (KBr) m/cm^{-1}: 3356, 1664, 1598, 1583, 1550, 1498, 1182, 1099. MS m/z (ESI): 451 $[M+H]^+$. Purity: 97.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.21. (E) -3-(4-((10-(dimethylamino)decyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide (8b)

Light yellow solid, yield: 67.3%, mp: 79.2-80.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24-1.50 (16H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 2.15 (6H, s, 2×$NCH_3$), 2.23-2.26 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 3.97-4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.68-6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99-7.07 (2H, m, Ar-H), 7.15-7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30-7.34 (2H, J = 16.0 Hz, Ar-H), 7.50-7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.68-7.70 (2H, d, J = 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 25.8, 26.4, 27.2, 28.9, 29.2, 29.3(2), 44.5(2), 51.5, 56.0, 59.2, 68.9, 110.4, 112.5, 119.9, 122.2(2), 124.2, 127.6(2), 129.0, 138.4, 142.0, 149.5(2), 150.4, 164.4. IR (KBr) m/cm^{-1}: 3360, 1681, 1602, 1585, 1554, 1489, 1174, 1078. MS m/z (ESI): 453 $[M+H]^+$. Purity: 97.7% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.22. (E) -3-(4-((10-(diethylamino)decyl)oxy)-3-methoxyphenyl)-N-phenylacrylamide(8c)

Light yellow solid, yield: 54.2%, mp: 76.3–78.2°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.06–1.09 (6H, t, J = 12.0 Hz, 2 × NCH_2CH_3), 1.24–1.50 (16H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 2.81 (6H, t, J = 12.0 Hz, 3 × NCH_2), 3.83 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.70–6.74 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.01–7.08 (2H, m, Ar-H), 7.16–7.18 (1H, d, J = 8.0 Hz, Ar-H), 7.22 (1H, s, Ar-H), 7.31–7.35 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.13 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.3(2), 25.9, 26.5, 27.7, 29.0, 29.3, 29.4, 29.5, 29.6, 46.8(2), 52.0, 55.9, 69.0, 110.3, 112.4, 119.9, 122.2(2), 124.2, 127.5(2), 129.0, 138.3, 142.2, 149.4(2), 150.4, 164.5.IR (KBr) m/cm^{-1}: 3305, 1680, 1602, 1583, 1550, 1498, 1174, 1078. MS m/z (ESI): 482 $[M+H]^+$. Purity: 98.2% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.23. (E)-3-(3-methoxy-4-((10-(piperidin-1-yl)decyl)oxy)phenyl)-N-phenylacrylamide(8d)

Pink solid, yield: 71.8%, mp: 94.2–95.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24–1.50 (26H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ and piperidine-H), 1.70–1.73 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.68–7.70 (2H, d, J = 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 24.2, 25.5(2), 25.9, 26.5, 27.6, 28.9, 29.3, 29.4, 29.5, 53.5, 54.5(2), 56.0, 59.4, 69.0, 110.3, 112.4, 119.9, 122.3(2), 124.3, 127.4(2), 129.1, 138.3, 142.3, 149.5(2), 150.5, 165.0. IR (KBr) m/cm^{-1}: 1678, 1598, 1581, 1552, 1498, 1178, 1078. MS m/z (ESI): 493 $[M+H]^+$. Purity: 97.6% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.8.24. (E)-3-(3-methoxy-4-((10-(pyrrolidin-1-yl)decyl)oxy)phenyl)-N-phenylacrylamide (8e)

Pink solid, yield: 53.2%, mp: 99.7–101.5°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm): 1.24–1.50 (24H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ and pyrrolidine-H), 1.70–1.73 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.82 (3H, s, OCH_3), 3.97–4.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.68–6.72 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.99–7.07 (2H, m, Ar-H), 7.15–7.17 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, s, Ar-H), 7.30–7.34 (2H, J = 16.0 Hz, Ar-H), 7.50–7.54 (1H, d, J = 16.0 Hz, Ar-CH=CH), 7.69–7.71 (2H, d, 8.0 Hz, Ar-H), 10.10 (1H, s, NH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.3(2), 25.9, 26.6, 27.7, 29.0, 29.3, 29.4, 29.5, 29.6, 16.8(2), 52.8, 55.9, 69.0, 110.3, 112.4, 119.8, 122.2(2), 124.2127.5(2), 129.1, 138.3, 142.2, 149.4, 150.1, 165.9.IR (KBr) m/cm^{-1}: 3284, 1695, 1602, 1583, 1552, 1498, 1176, 1080. MS m/z (ESI): 479 $[M+H]^+$. Purity: 98.5% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9. Synthesis of compound 9a-9c, and 10c

4.9.1. (E)-ethyl 3-(4-((6-bromohexyl)oxy)-3-methoxyphenyl) acrylate (9a)

Ethyl ferulate (compound **6**) was synthesized as described previously [20]. Then compound **6** was treated with 1,6-dibromohexane (2.8 mL, 15 mmol) according to the general procedure to achieve compound **9a** with a yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30–1.40 (5H, m, $OCH_2CH_2CH_2CH_2CH_2$ and CH_3CH_2O), 1.45–1.50 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.83–1.90 (2H, m, $OCH_2CH_2CH_2CH_2CH_2$), 2.43–2.46 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.89 (3H, s, OCH_3), 4.03–4.06 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 4.23–4.28 (2H, t, CH_3CH_2O), 6.28–6.32 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.84–6.86 (1H, d, J = 8.0 Hz, Ar-H), 7.05–7.07 (1H, d, J = 8.0 Hz, Ar-H), 7.09 (1H, s, Ar-H), 7.60–7.64 (1H, d, J = 16.0 Hz, Ar-CH=CH). MS m/z (ESI): 385 $[M+H]+$. Purity: 97.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9.2. (E)-ethyl 3-(4-((8-bromooctyl)oxy)-3-methoxyphenyl) acrylate (10a)

Compound **6** was treated with 1,8-dibromooctane (3.1 mL, 15 mmol) according to the general procedure to achieve compound **10a** with a yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.35 (5H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ and CH_3CH_2O), 1.67 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 1.77–1.80 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 2.83–2.87 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.00–3.05 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.83 (3H, s, OCH_3), 3.90–3.93 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2), 4.23–4.28 (2H, t, CH_3CH_2O), 6.38–6.42 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.68–6.70 (1H, d, J = 8.0 Hz, Ar-H), 6.96–6.98 (1H, d, J = 8.0 Hz, Ar-H), 7.04 (1H, s, Ar-H), 7.42–7.46 (1H, d, J = 16.0 Hz, Ar-CH=CH), 11.25 (1H, s, COOH). MS m/z (ESI): 413 $[M+H]+$. Purity: 97.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9.3. (E)-ethyl-3-(4-((6-(diethylamino)hexyl)oxy)-3-methoxyphenyl)acrylate (9c)

Compound 9c was synthesized by the method mentioned above. Pale yellow viscous liquid, ′yield 56.3%; 1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.02–1.06 (6H, t, J = 12.0 Hz, 2 × NCH_2CH_3), 1.30–1.40 (5H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$ and CH_3CH_2O), 1.45–1.50 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.83–1.90 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.43–2.46 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$2.53–2.58 (4H, m, 2 × NCH_2CH_3), 3.89 (3H, s, OCH_3), 4.03–4.06 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 4.23–4.28 (2H, t, CH_3CH_2O), 6.28–6.32 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.84–6.86 (1H, d, J = 8.0 Hz, Ar-H),

7.05–7.07 (1H, d, J = 8.0 Hz, Ar-H), 7.09 (1H, s, Ar-H), 7.60–7.64 (1H, d, J = 16.0 Hz, Ar-CH=CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.7(2), 14.4, 25.9, 26.9, 27.9, 29.0, 46.9(2), 52.9, 55.9, 60.3, 68.9, 110.4, 112.3, 115.8, 122.5, 127.3, 144.6, 149.5, 150.7, 167.3.IR (KBr) m/cm^{-1}: 2935, 1770, 1598, 1581, 1510, 1257, 1161, 1093. MS m/z (ESI): 378 $[M+H]^+$. Purity: 98.9% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9.4. (E)-ethyl-3-(3-methoxy-4-((6-(piperidin-1-yl)hexyl)oxy) phenyl)acrylate (9d)

Light yellow solid, yield 63.8%, mp: 72.6–73.8°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30–1.38 (5H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$ and CH_3CH_2O), 1.45–1.51 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.57–1.65 (6H, m, piperidine-H), 1.82–1.87 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.44 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$) 2.53–2.58 (4H, m, piperidine-H), 3.89 (3H, s, OCH_3), 4.02–4.05 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 4.23–4.28 (2H, t, CH_3CH_2O), 6.28–6.32 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.84–6.86 (1H, d, J = 8.0 Hz, Ar-H), 7.05–7.07 (1H, d, J = 8.0 Hz, Ar-H), 7.09 (1H, s, Ar-H), 7.60–7.64 (1H, d, J = 16.0 Hz, Ar-CH=CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 14.4, 24.2, 25.6(2), 25.9, 26.4, 27.4, 28.9, 54.5(2), 55.9, 59.3, 60.3, 68.9, 110.1, 112.4, 115.8, 122.6, 127.3, 144.6, 149.5, 150.7, 167.3. IR (KBr) m/cm^{-1}: 2935, 1693, 1597, 1577, 1510, 1267, 1165, 1101. MS m/z (ESI): 390 $[M+H]^+$. Purity: 98.2% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9.5. (E)-ethyl-3-(3-methoxy-4-((6-(pyrrolidin-1-yl)hexyl)oxy) phenyl)acrylate (9e)

Light yellow solid, yield 57.5%, mp: 86.8-87.6°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.32-1.35 (3H, t, J = 12.0 Hz, CH_3CH_2O), 1.38-1.42 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.46-1.49 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.55-1.58 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.79 (4H, m, pyrrolidine-H), 1.83-1.88 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.43-2.47 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.51 (4H, m, pyrrolidine-H), 3.89 (3H, s, OCH_3), 4.03-4.06 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 4.23-4.28 (2H, t, CH_3CH_2O), 6.28-6.32 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.84-6.86 (1H, d, J = 8.0 Hz, Ar-H), 7.05-7.07 (1H, d, J = 8.0 Hz, Ar-H), 7.09 (1H, s, Ar-H), 7.60-7.64 (1H, d, J = 16.0 Hz, Ar-CH=CH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 14.4, 23.4(2), 25.9, 27.5, 28.9, 29.0, 54.3(2), 55.9, 56.9, 60.4, 68.9, 110.0, 112.3, 115.8, 122.6, 127.3, 144.6, 149.5, 150.7, 167.3. IR (KBr) m/cm^{-1}: 2935, 1747, 1597, 1577, 1510, 1247, 1165, 1101. MS m/z (ESI): 376 $[M+H]^+$. Purity: 99.0% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.9.6. (E)-ethyl-3-(4-((8-(diethylamino)octyl)oxy)-3-methoxyphenyl)acrylate (10c)

Compound **10c** was synthesized by the similar method mentioned above. Pale yellow viscous liquid, yield 54.2%; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23–1.27 (6H, t, J = 16.0 Hz, 2 × NCH_2CH_3), 1.35 (5H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$ and CH_3CH_2O), 1.67 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 1.77–1.80 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 2.83–2.87 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2$), 3.00–3.05 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$ CH_2CH_2), 3.12 (4H, m, 2 × NCH_2CH_3), 3.83 (3H, s, OCH_3), 3.90–3.93 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2$ $CH_2CH_2CH_2$ CH_2CH_2), 4.23–4.28 (2H, t, CH_3CH_2O), 6.38–6.42 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.68–6.70 (1H, d, J = 8.0 Hz, Ar-H), 6.96–6.98 (1H, d, J = 8.0 Hz, Ar-H), 7.04 (1H, s, Ar-H), 7.42–7.46 1H, d, J = 16.0 Hz, Ar-CH=CH. ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 11.7(2), 14.4, 25.9, 26.9, 27.9, 29.0(3), 46.9(2), 52.9, 55.9, 60.3, 68.9, 110.4, 112.3, 115.8, 122.5, 127.3, 144.6, 149.5, 150.7, 167.3.IR (KBr) m/cm^{-1}: 2937, 1708, 1625, 1599, 1512, 1263, 1180, 1018. MS m/z (ESI): 406 $[M+H]^+$. Purity: 98.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.10. General procedure for the synthesis of compounds 11c-11e and 12c

Compounds **11c-11e** and **12c** were synthesized from compounds **9c-9e** and **10c,** respectively. Compounds **9c-9e** and **10c** were hydrolyzed by NaOH solution stirring on a cooled bath in absolute ethyl alcohol. After the solvent was removed under reduced pressure, 10% ice-hydrochloric acid was added to adjust the solution to pH = 6–7, then the crude product was partitioned by ethyl acetate (3 × 30 mL), dried over anhydrous Na_2SO_4 and evaporated in vacuum. The obtained residue was purified by silica gel chromatography with different ratio of CH_2Cl_2/MeOH as eluent to generate target compounds **11c-11e** and **12c** with a yield of 60–75%.

4.10.1. (E)-3-(4-((6-(diethylamino)hexyl)oxy)-3-methoxyphenyl) acrylic acid (11c)

Light yellow solid, yield 63.4%, mp: 146.3–147.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.44–1.47 (6H, t, J = 12.0 Hz, 2 × NCH_2CH_3), 1.55–1.57 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.85–1.90 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.00 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$) 3.16 (4H, m, 2 × NCH_2CH_3), 3.90 (3H, s, OCH_3), 4.04–4.07 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.30–6.34 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.86–6.88 (1H, d, J = 8.0 Hz, Ar-H), 7.07 (1H, s, Ar-H), 7.10–7.12 (1H, d, J = 8.0 Hz, Ar-H), 7.69–7.73 (1H, d, J = 16.0 Hz, Ar-CH=CH), 10.71 (1H, s, COOH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 23.3(2), 25.4, 25.5, 28.7, 53.7(2), 55.1, 59.9, 68.5, 110.3, 112.4, 114.9, 123.1, 127.0, 146.8, 149.5, 150.9, 171.7. IR (KBr) m/cm¬-1: 3340, 2937, 1708, 1598, 1510, 1213, 1246, 1013. MS m/z (ESI): 350 $[M+H]^+$. Purity: 98.3% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.10.2. (E)-3-(3-methoxy-4-((6-(piperidin-1-yl)hexyl)oxy)phenyl) acrylic acid (11d)

Light yellow solid, yield 71.3%, mp: 151.0–152.9°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.30–1.38 (3H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.45–1.51 (4H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.57–1.65 (6H, m, piperidine-H), 1.82–1.87 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.53–2.58 (4H, m, piperidine-H), 3.57–3.60 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.90 (3H, s, OCH_3), 4.04–4.07 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.30–6.34 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.86–6.88 (1H, d, J = 8.0 Hz, Ar-H), 7.07 (1H, s, Ar-H), 7.10–7.12 (1H, d, J = 8.0 Hz, Ar-H), 7.69–7.73 (1H, d, J = 16.0 Hz, Ar-CH=CH), 10.71 (1H, s, COOH)· ^{13}C NMR (400 MHz, CDCl3) δ (ppm): 8.9(2), 23.8, 25.8, 26.9, 29.0(2), 29.1, 45.4(2), 50.7, 55.9, 68.8, 109.9, 112.4, 121.6, 122.6, 128.9, 140.1, 149.3, 149.4, 173.2.IR (KBr) m/cm-1:3331, 2937, 1738, 1577, 1523, 1226, 1218, 1013. MS m/z (ESI): 362 $[M+H]+$. Purity: 98.8% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.10.3. (E)-3-(3-methoxy-4-((6-(pyrrolidin-1-yl)hexyl)oxy)phenyl) acrylic acid (11e)

Light yellow solid, yield 60.5%, mp: 165.3–166.9°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.38–1.42 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.46–1.49 (2H, m, $OCH_2CH_2CH_2$ $CH_2CH_2CH_2$), 1.55–1.58 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 1.79 (4H, m, pyrrolidine-H), 1.83–1.88 (2H, m, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 2.51 (4H, m, pyrrolidine-H), 3.57–3.60 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 3.90 (3H, s, OCH_3), 4.03–4.06 (2H, t, J = 12.0 Hz, $OCH_2CH_2CH_2CH_2CH_2CH_2$), 6.29–6.33 (1H, d, J = 16.0 Hz, Ar-CH=CH), 6.85–6.87 (1H, d, J = 8.0 Hz, Ar-H), 7.07 (1H, s, Ar-H), 7.10–7.12 (1H, d, J = 8.0 Hz, Ar-H), 7.69–7.73 (1H, d, J = 16.0 Hz, Ar-CH=CH), 11.25 (1H, s, COOH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 23.4(2), 25.4, 25.5, 28.7, 53.7(2), 55.1, 56.0, 68.5, 110.3, 112.4, 114.9, 123.1, 127.0, 146.8, 149.5, 150.9, 171.7. IR (KBr) m/cm^{-1}: 3332, 2935,

1732, 1635, 1579, 1541, 1213, 1138. MS *m/z* (ESI): 348 $[M+H]^+$. Purity: 99.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.10.4. (E)-3-(4-((8-(diethylamino)octyl)oxy)-3-methoxyphenyl) acrylic acid (12c)

Light yellow solid, yield 71.4%, mp: 86.6–88.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.23–1.27 (6H, t, J = 16.0 Hz, 2 × $NCH_2\underline{CH_3}$), 1.35 (2H, m, $OCH_2CH_2CH_2CH_2\underline{CH_2}CH_2CH_2CH_2$), 1.67 (2H, m, $\overline{OCH_2}CH_2CH_2\underline{CH_2}CH_2CH_2CH_2CH_2$), 1.77–1.80 (2H, m, $OCH_2CH_2CH_2CH_2CH_2\underline{CH_2}\overline{CH_2}CH_2$), 2.83–2.87 (4H, m, $OCH_2CH_2\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}CH_2$), 3.00–3.05 (4H, m, $OCH_2\underline{CH_2}CH_2CH_2CH_2\underline{CH_2}CH_2\underline{CH_2}$), 3.12 (4H, m, 2 × $NC\underline{H_2}CH_3$), 3.83 (3H, s, $O\underline{CH_3}$), 3.90–3.93 (2H, t, J = 12.0 Hz, $OC\underline{H_2}CH_2CH_2CH_2CH_2CH_2$ $CH_2\underline{CH_2}$), 6.38–6.42 (1H, d, J = 16.0 Hz, Ar-$\underline{CH}$=$C\underline{H}$), 6.68–6.70 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 6.96–6.98 (1H, d, J = 8.0 Hz, Ar-$\underline{H}$), 7.04 (1H, s, Ar-$\underline{H}$), 7.42–7.46 (1H, d, J = 16.0 Hz, Ar-$\underline{CH}$=CH), 11.25 (1H, s, COOH). ^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm): 8.9(2), 23.8, 25.8, 26.9, 29.0(2), 29.1, 45.4(2), 50.7, 55.9, 68.8, 109.9, 112.4, 121.6, 122.6, 128.9, 140.1, 149.3, 149.4, 173.2. IR (KBr) m/cm^{-1}: 3330, 2933, 1711, 1633, 1579, 1541, 1318, 1130. MS *m/z* (ESI): 378 $[M+H]^+$. Purity: 99.1% by HPLC (MeOH/0.1% TEA 85:15 (v/v)).

4.11. Cholinesterase and carboxylesterase (CaE) inhibitory activity assays

The effects of the newly synthesized compounds on AChE/BuChE were measured by the modified *Ellmann* method [21]. The individual compound was dissolved in Tween 80 and diluted with water to obtain five different concentrations before use. All reactions were performed in triplicate. The assay mixture contained 100 μL AChE or BuChE, 100 μL acetylthiocholine iodide or butyrylthiocholine iodide, 2.76 mL phosphoric acid buffer (pH 8.0, 0.1 mol/L) and 100 μL different concentrations of test compounds. The mixture was incubated for 25 min (30 °C), and terminated by adding 100 μL 20% sodium dodecyl sulfate (SDS), followed by adding 100 μL 10 mmol/L 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB) to generate the yellow anion 5-thio-2-nitro-benzoic acid. The hydrolysis of acetylthiocholine or butyrylthiocholine was monitored at 412 nm by UV spectroscopy. The IC_{50} values were calculated by Bliss method. Rivastigmine was used as positive reference compound.

The assay of CaE was conducted by previous reported method with some modifications [22]. The assay solution consisted of 100 mmol/L potassium phosphate buffer(pH 8.0, 25 °C), 1.0 mmol/L 4-nitrophenyl acetate and adequate amount of CaE. Following by the hydrolysis of 4-nitrophenyl acetate induced by CaE, 4-nitrophenol released and determined by UV-Vis spectrophotometer at 405 nm, and the activity of CaE was proportional to the concentration of .4-nitrophenol.

4.12. Kinetic assay

Kinetic assay was conducted on compound **6d** by a modified method to obtain further information on the possible action mechanism of the newly synthesized compounds on AChE and BuChE [23]. Compound **6d** was added into the assay solution and pre-incubated with the enzyme at 30 °C, followed by the addition of 100 μL acetylthiocholine iodide including five concentrations of compound **6d**, respectively. The assay solution contained 100 μL compound **6d**, 100 μL DTNB, phosphoric acid buffer (pH 8.0, 0.1 mol/L). The hydrolysis of acetylthiocholine iodide catalyzed by AChE was measured at 412 nm by UV spectroscopy. Additionally, the parallel control experiment was performed without compound **6d** in the assay solution.

4.13. Molecular docking

Molecular docking study was carried out using Molecular Operating Environment (MOE) software package. The X-ray crystallographic structures of AChE (PDB code: 1EVE) and BuChE (PDB code: 1P0I) were provided by protein data bank [24]. Subsequently, compound **6d** was docked using the optimized parameters.

4.14. Log P measurement

Octanol-water partition coefficients of new synthesized compounds were measured by the shake flask method described previously [25,26]. The aqueous phase was replaced by PBS (pH = 7.4). The assay mixture containing test compounds was shaken at 37 °C over night and then centrifuged at 2000 rpm for 20 min, followed by the analysis with HPLC. A C_{18} column (150 nm × 4.6 mm, 5 μm) was used with the mobile phase of methanol-0.1% triethylamine (TEA) (85:15, v/v) at a flow rate of 1.0 mL.min^{-1} and the detection wavelength of 322 nm at 32 °C. Experiments were conducted in triplicate and log P values were calculated.

Declaration of interest

The authors have declared no conflict of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2016.12.003.

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