Supplementary Information

Multitarget-directed resveratrol derivatives: anti-cholinesterases, anti-β-amyloid aggregation and monoamine oxidase inhibition properties against Alzheimer’s disease

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Experimental

General

All common reagents and solvents were obtained from commercial suppliers and used without further purification. Reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF$_{254}$ plates (Qingdao Haiyang Chemical Plant, Qingdao, China) plates and the spots were detected under UV light (254 nm). Column chromatography was performed on silica gel (90-150 μm; Qingdao Marine Chemical Inc.) IR (KBr discs) spectra were recorded on a Bruker Tensor 27 spectrometer (Bruker, Karlsruhe, Germany). Melting point was measured on an XT-4 micromelting point instrument and uncorrected. $^1$H NMR and $^{13}$C NMR spectra were measured on a Bruker ACF-500 spectrometer at 25 °C and referenced to TMS. Chemical shifts are reported in ppm ($\delta$) using the residual solvent line as internal standard. The purity of all compounds used for biological evaluation was confirmed to be higher than 97% through analytical HPLC performed with Agilent 1200 HPLC System. A Zorbax SB-C$_{18}$ column (4.6 mm × 250 mm, 5 μm, Agilent, Inc.) was used. The mobile phase was 0.01% THF water solution (A) and MeOH (B) gradient system and the flow rate was 1.0 mL/min with the gradient: 0-20 min, 60% B to 90% B. Mass spectra were obtained on a MS Agilent 1100 Series LC/MSD Trap mass spectrometer (ESI-MS) and a Mariner ESI-TOF spectrometer (HRESI-MS), respectively.

1-(Bromomethyl)-3,5-dimethoxybenzene (2)

PBr$_3$ (1.8 ml) was added dropwise to a solution of (3,5-dimethoxyphenyl)methanol (3.26 g, 19.4 mmol) and pyridine (0.078 ml) in CH$_2$Cl$_2$ at 0 °C. After the mixture was
slowly warmed to room temperature and stirred for 4 h, the reaction was quenched by the slowly addition of ice water, extracted with CH₂Cl₂, washed with brine, dried over Na₂SO₄ and concentrated to provide 1-(bromomethyl)-3,5-dimethoxybenzene as white solid, yield 96%. ¹H NMR (500 MHz, MEOD) δ 6.57 (d, J = 2.5 Hz, 2H), 6.41 (t, J = 2.5 Hz, 1H), 4.48 (s, 2H), 3.77 (s, 6H); MS (ESI) m/z 230.0 [M+H]⁺.

**Diethyl 3,5-dimethoxybenzylphosphonate (3)**

The mixture of 2 (2.17 g, 39.4 mmol) and triethyl phosphate (4.5 ml) were heated at 160 °C for 4 h. The excess triethyl phosphate was removed in vacuum to provide the crude product as a colorless oil, yield 95%. ¹H NMR (500 MHz, CDCl₃): δ 6.46 (t, J = 2.5 Hz, 2H), 6.35 (d, J = 2.5 Hz, 1H), 4.05-4.02 (m, 4H), 3.77 (s, 6H), 3.09 (d, J = 21.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 6H); MS (ESI) m/z 288.0 [M+H]⁺.

**General procedures for the preparation of intermediate (4a-g)**

To a stirred mixture of 4-hydroxybenzaldehyde (5 mmol) and K₂CO₃ (1.4 g, 10 mmol) in acetonitrile (15 mL), α,ω-dibromoalkanes (25 mmol) was added. After stirred for 4 h at 40 °C, the mixture was filtered and the filtrate was evaporated under reduced pressure. The obtained residue was purified by silica gel chromatography with petroleum/ethyl acetate as an eluent to give compounds 4a-g.

**4-(2-Bromoethoxy)benzaldehyde (4a)**

4-Hydroxybenzaldehyde was treated with 1,2-dibromoethane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (15:1, v/v) as elution solvent to obtain the desired product 4a as a light yellow solid, yield 85.5%, mp 50-52 °C. ¹H NMR
(500 MHz, DMSO-$d_6$) $\delta$ 9.91 (s, 1H), 7.90 (d, $J = 8.5$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 4.47 (t, $J = 5.5$ Hz, 2H), 3.87 (t, $J = 5.5$ Hz, 2H); MS (ESI) $m/z$ 230.0 [M+H]$^+$.  

4-(3-Bromopropoxy)benzaldehyde (4b) 

4-Hydroxybenzaldehyde was treated with 1,3-dibromopropane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 4b as a light yellow solid, yield 88.6%, mp 31-32 ºC. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.90 (s, 1H), 7.99 (d, $J = 8.5$ Hz, 2H), 7.17 (d, $J = 9.0$ Hz, 2H), 4.23 (t, $J = 6.0$ Hz, 2H), 3.70 (t, $J = 6.5$ Hz, 2H), 2.34-2.28 (m, 2H); MS (ESI) $m/z$ 244.0 [M+H]$^+$.  

4-(4-Bromobutoxy)benzaldehyde (4c) 

4-Hydroxybenzaldehyde was treated with 1,4-dibromobutane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (20:1, v/v) as elution solvent to obtain the desired product 4c as a light yellow solid, yield 86.0%, mp 32-34 ºC. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.89 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.15 (d, $J = 9.0$ Hz, 2H), 4.16 (t, $J = 6.5$ Hz, 2H), 3.64 (t, $J = 6.5$ Hz, 2H), 2.03-1.95 (m, 2H), 1.92-1.86 (m, 2H); MS (ESI) $m/z$ 258.1 [M+H]$^+$.  

4-((5-Bromopentyl)oxy)benzaldehyde (4d) 

4-Hydroxybenzaldehyde was treated with 1,5-dibromopentane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (20:1, v/v) as elution solvent to obtain
the desired product 4d as a white solid, yield 78.5%, mp 35-36 ºC. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.89 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.14 (d, $J = 9.0$ Hz, 2H), 4.12 (t, $J = 6.5$ Hz, 2H), 3.58 (t, $J = 6.5$ Hz, 2H), 1.92-1.87 (m, 2H), 1.82-1.76 (m, 2H), 1.60-1.53 (m, 2H); MS (ESI) m/z 272.3 [M+H]$^+$. 

4-((6-Bromohexyl)oxy)benzaldehyde (4e)

4-Hydroxybenzaldehyde was treated with 1,6-dibromohexane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 4e as a white solid, yield 76.6%, mp 39-40 ºC. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.88 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 2H), 7.14 (d, $J = 8.5$ Hz, 2H), 4.11 (t, $J = 6.5$ Hz, 2H), 3.56 (t, $J = 6.5$ Hz, 2H), 1.88-1.75 (m, 4H), 1.48-1.46 (m, 4H); MS (ESI) m/z 284.4 [M-H]$^+$.

4-((7-Bromoheptyl)oxy)benzaldehyde (4f)

4-Hydroxybenzaldehyde was treated with 1,7-dibromohexane according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (20:1, v/v) as elution solvent to obtain the desired product 4f as a pale yellow solid, yield 74.3%, mp 42-42 ºC. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.88 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 2H), 7.14 (d, $J = 9.0$ Hz, 2H), 4.11 (t, $J = 6.5$ Hz, 2H), 3.56 (t, $J = 6.5$ Hz, 2H), 1.86-1.75 (m, 4H), 1.48-1.29 (m, 6H); MS (ESI) m/z 299.1 [M+H]$^+$.

4-((8-Bromooctyl)oxy)benzaldehyde (4g)

4-Hydroxybenzaldehyde was treated with 1,8-dibromohexane according to the
general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (15:1, v/v) as elution solvent to obtain the desired product 4g as a pale yellow solid, yield 72.4%, mp 46-48 °C. 1H NMR (500 MHz, DMSO-d6) δ 9.88 (s, 1H), 7.88 (d, J = 9.0 Hz, 2H), 7.14 (d, J = 9.0 Hz, 2H), 4.11 (t, J = 6.5 Hz, 2H), 3.56 (t, J = 6.5 Hz, 2H), 1.83-1.75 (m, 4H), 1.47-1.29 (m, 8H); MS (ESI) m/z 314.2 [M+H]+.

**General procedures for the preparation of intermediate (5a-v)**

To a stirred mixture of 4a-g (0.5 mmol) and K2CO3 (0.14 g, 1 mmol) in acetonitrile (10 mL), amine (1 mmol) was added and the mixture was refluxed for 8 h. After cooling to the room temperature, the mixture was filtered and the filtrate was evaporated under vacuum. The obtained residue was purified by silica gel chromatography with petroleum/acetone as eluent to give target compounds 5a-v.

**4-(2-(Benzyl(methyl)amino)ethoxy)benzaldehyde (5a)**

Intermediate 4a was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain the desired product 5a as a light yellow oil, yield 78.2%. 1H NMR (500 MHz, DMSO-d6) δ 9.89 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.33 (d, J=4.5 Hz, 4H), 7.28-7.24 (m, 1H), 7.15 (d, J = 8.5 Hz, 2H), 4.24 (t, J = 6.5 Hz, 2H), 3.59 (s, 2H), 2.79 (t, J = 6.0 Hz, 2H), 2.26 (s, 3H); MS (ESI) m/z 270.2 [M+H]+.

**4-(3-(Benzyl(methyl)amino)propoxy)benzaldehyde (5b)**

Intermediate 4b was treated with N-methyl-1-phenylmethanamine according to the
general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (20:1, v/v) as elution solvent to obtain the desired product 5b as a light yellow oil, yield 80.0%. ¹H NMR (500 MHz, DMSO- $d_6$) $\delta$ 9.89 (s, 1H), 7.88 (d, $J = 9.0$ Hz, 2H), 7.28 (d, $J = 4.5$ Hz, 4H), 7.25-7.21 (m, 1H), 7.11 (d, $J = 8.5$ Hz, 2H), 4.15 (t, $J = 6.5$ Hz, 2H), 3.49 (s, 2H), 2.50 (t, $J = 7.0$ Hz, 2H), 2.17 (s, 3H), 1.96-1.92 (m, 2H); MS (ESI) m/z 284.2 [M+H]⁺.

4-(4-(Benzyl(methyl)amino)butoxy)benzaldehyde (5c)

Intermediate 4c was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (15:1, v/v) as elution solvent to obtain the desired product 5c as a light yellow oil, yield 75.9%. ¹H NMR (500 MHz, DMSO- $d_6$) $\delta$ 9.89 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.34-7.29 (m, 4H), 7.26-7.23 (m, 1H), 7.12 (d, $J = 8.5$ Hz, 2H), 4.10 (t, $J = 6.5$ Hz, 2H), 3.47 (s, 2H), 2.39 (t, $J = 7.0$ Hz, 2H), 2.12 (s, 3H), 1.81-1.76 (m, 2H), 1.66-1.60 (m, 2H); MS (ESI) m/z 298.3 [M+H]⁺.

4-((5-(Benzyl(methyl)amino)pentyl)oxy)benzaldehyde (5d)

Intermediate 4d was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (5:1, v/v) as elution solvent to obtain the desired product 5d as a light yellow oil, yield 77.2%. ¹H NMR (500 MHz, DMSO- $d_6$) $\delta$ 9.88 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.34-7.29 (m, 4H), 7.26-7.23 (m, 1H), 7.13 (d, $J = 8.5$ Hz, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 3.45 (s, 2H), 2.34 (t, $J = 7.0$ Hz, 2H), 2.11 (s, 3H), 1.78-1.72 (m, 2H), 1.57-1.51 (m, 2H), 1.48-1.42 (m, 2H); MS (ESI) m/z
312.3 [M+H]⁺.

4-((6-(Benzyl(methyl)amino)hexyl)oxy)benzaldehyde (5e)

Intermediate 4e was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (10:1, v/v) as elution solvent to obtain the desired product 5e as a light yellow oil, yield 75.4%. ¹H NMR (500 MHz, DMSO-d₆) δ 9.88 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.33-7.29 (m, 4H), 7.25-7.23 (m, 1H), 7.13 (d, J = 8.5 Hz, 2H), 4.08 (t, J = 6.5 Hz, 2H), 3.44 (s, 2H), 2.33 (t, J = 7.0 Hz, 2H), 2.11 (s, 3H), 1.76-1.72 (m, 2H), 1.50-1.34 (m, 6H); MS (ESI) m/z 326.4 [M+H]⁺.

4-((7-(Benzyl(methyl)amino)heptyl)oxy)benzaldehyde (5f)

Intermediate 4f was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (15:1, v/v) as elution solvent to obtain the desired product 5f as a light yellow oil, yield 78.5%. ¹H NMR (500 MHz, DMSO-d₆) δ 9.88 (s, 1H), 7.87 (d, J = 8.5 Hz, 2H), 7.33-7.29 (m, 4H), 7.26-7.23 (m, 1H), 7.13 (d, J = 8.5 Hz, 2H), 4.08 (t, J = 6.5 Hz, 2H), 3.44 (s, 2H), 2.32 (t, J = 7.0 Hz, 2H), 2.11 (s, 3H), 1.76-1.72 (m, 2H), 1.50-1.34 (m, 8H); MS (ESI) m/z 340.3 [M+H]⁺.

4-((8-(Benzyl(methyl)amino)octyl)oxy)benzaldehyde (5g)

Intermediate 4g was treated with N-methyl-1-phenylmethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (10:1, v/v) as elution solvent to obtain the desired product 5g as a light yellow oil, yield 76.8%. ¹H NMR (500 MHz, DMSO-
δ 9.88 (s, 1H), 7.88 (d, \( J = 8.5 \) Hz, 2H), 7.33-7.28 (m, 4H), 7.25-7.22 (m, 1H),
7.13 (d, \( J = 8.5 \) Hz, 2H), 4.09 (t, \( J = 6.5 \) Hz, 2H), 3.44 (s, 2H), 2.30 (t, \( J = 7.0 \) Hz, 2H),
2.10 (s, 3H), 1.76-1.73 (m, 2H), 1.50-1.34 (m, 10H); MS (ESI) \( m/z \) 354.4 [M+H]+.

**4-((6-(Benzyl(ethyl)amino)hexyl)oxy)benzaldehyde (5h)**

Intermediate 4e was treated with \( N \)-benzylethanamine according to the general
procedure to give a crude product. Then it was purified using silica gel
chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain
the desired product 5h as a light yellow oil, yield 74.5%. \(^1\)H NMR (500 MHz, DMSO-
\( d_6 \)) δ 9.88 (s, 1H), 7.87 (d, \( J = 8.5 \) Hz, 2H), 7.31-7.26 (m, 4H), 7.26-7.21 (m, 1H),
7.13 (d, \( J = 8.5 \) Hz, 2H), 4.08 (t, \( J = 6.5 \) Hz, 2H), 3.52 (s, 2H), 2.45 (t, \( J = 7.0 \) Hz, 2H),
2.39 (t, \( J = 7.0 \) Hz, 2H), 1.76-1.72 (m, 2H), 1.45-1.32 (m, 6H), 0.98 (s, 3H); MS (ESI)
\( m/z \) 340.4 [M+H]+.

**4-((6-(Ethyl(2-methoxybenzyl)amino)hexyl)oxy)benzaldehyde (5i)**

Intermediate 4e was treated with \( N \)-(2-methoxybenzyl)ethanamine according to the
general procedure to give a crude product. Then it was purified using silica gel
chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain
the desired product 5i as a colorless oil, yield 79.7%. \(^1\)H NMR (500 MHz, DMSO-
\( d_6 \)) δ 9.88 (s, 1H), 7.87 (d, \( J = 8.0 \) Hz, 2H), 7.36 (dd, \( J = 6.0 \) Hz, 1.5 Hz, 1H), 7.20 (m,
1H), 7.11 (d, \( J = 8.5 \) Hz, 2H), 6.95 (d, \( J = 8.5 \) Hz, 1H), 6.91 (t, \( J = 7.5 \) Hz, 1H), 4.08
(t, \( J = 6.5 \) Hz, 2H), 3.74 (s, 3H), 3.51 (s, 2H), 2.45 (q, \( J = 7.0 \) Hz, 2H), 2.40 (t, \( J = 7.5 
Hz, 2H), 1.76-1.70 (m, 2H), 1.48-1.31 (m, 6H), 0.99 (t, \( J = 7.0 \) Hz, 3H); MS (ESI) \( m/z \)
370.4 [M+H]+.
4-((6-(Ethyl(3-methoxybenzyl)amino)hexyl)oxy)benzaldehyde (5j)

Intermediate 4e was treated with N-(3-methoxybenzyl)ethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain the desired product 5j as a colorless oil, yield 76.5%. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 9.88 (s, 1H), 7.87 (d, \(J = 9.0\) Hz, 2H), 7.21 (t, \(J = 8.0\) Hz, 1H), 7.11 (d, \(J = 8.5\) Hz, 2H), 6.90-6.87 (m, 2H), 6.80-6.78 (m, 1H), 4.07 (t, \(J = 6.5\) Hz, 2H), 3.74 (s, 3H), 3.50 (s, 2H), 2.45 (q, \(J = 7.0\) Hz, 2H), 2.39 (t, \(J = 7.0\) Hz, 2H), 1.73-1.71 (m, 2H), 1.45-1.33 (m, 6H), 0.98 (t, \(J = 7.0\) Hz, 3H); MS (ESI) m/z 370.4 [M+H]⁺.

4-((6-(Ethyl(4-methoxybenzyl)amino)hexyl)oxy)benzaldehyde (5k)

Intermediate 4e was treated with N-(4-methoxybenzyl)ethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain the desired product 5k as a colorless oil, yield 74.3%. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 9.88 (s, 1H), 7.87 (d, \(J = 8.5\) Hz, 2H), 7.21 (d, \(J = 8.5\) Hz, 2H), 7.12 (d, \(J = 8.5\) Hz, 2H), 6.86 (d, \(J = 8.5\) Hz, 2H), 4.08 (t, \(J = 6.5\) Hz, 2H), 3.73 (s, 3H), 3.45 (s, 2H), 2.43 (q, \(J = 7.0\) Hz, 2H), 2.37 (t, \(J = 7.5\) Hz, 2H), 1.75-1.70 (m, 2H), 1.45-1.31 (m, 6H), 0.97 (t, \(J = 7.0\) Hz, 3H); MS (ESI) m/z 370.4 [M+H]⁺.

4-((6-(Ethyl(2-fluorobenzyl)amino)hexyl)oxy)benzaldehyde (5l)

Intermediate 4e was treated with N-(2-fluorobenzyl)ethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain
the desired product 5l as a colorless oil, yield 72.0%. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.88 (s, 1H), 7.87 (d, $J = 8.5$ Hz, 2H), 7.45-7.41 (m, 1H), 7.31-7.26 (m, 1H), 7.18-7.10 (m, 4H), 4.07 (t, $J = 6.5$ Hz, 2H), 3.57 (s, 2H), 2.45 (q, $J = 7.0$ Hz, 2H), 2.40 (t, $J = 7.0$ Hz, 2H), 1.76-1.70 (m, 2H), 1.48-1.30 (m, 6H), 0.99 (t, $J = 7.0$ Hz, 3H); MS (ESI) m/z 358.4 [M+H]$^+$. 

4-((6-(Ethyl(3-fluorobenzyl)amino)hexyl)oxy)benzaldehyde (5m)

Intermediate 4e was treated with N-(3-fluorobenzyl)ethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain the desired product 5m as a colorless oil, yield 73.3%. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.88 (s, 1H), 7.87 (d, $J = 9.0$ Hz, 2H), 7.37-7.32 (m, 1H), 7.16-7.10 (m, 4H), 7.06-7.02 (m, 1H), 4.07 (t, $J = 6.5$ Hz, 2H), 3.54 (s, 2H), 2.45 (q, $J = 7.0$ Hz, 2H), 2.39 (t, $J = 7.0$ Hz, 2H), 1.76-1.70 (m, 2H), 1.48-1.30 (m, 6H), 0.98 (t, $J = 7.0$ Hz, 3H); MS (ESI) m/z 358.4 [M+H]$^+$. 

4-((6-(Ethyl(4-fluorobenzyl)amino)hexyl)oxy)benzaldehyde (5n)

Intermediate 4e was treated with N-(4-fluorobenzyl)ethanamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (6:1, v/v) as elution solvent to obtain the desired product 5n as a colorless oil, yield 70.0%. $^1$H NMR (500 MHz, DMSO-$d_6$) δ 9.88 (s, 1H), 7.89-7.85 (m, 2H), 7.35-7.33 (m, 2H), 7.14-7.10 (m, 4H), 4.08 (t, $J = 6.5$ Hz, 2H), 3.50 (s, 2H), 2.44 (q, $J = 7.0$ Hz, 2H), 2.38 (t, $J = 7.5$ Hz, 2H), 1.76-1.71 (m, 2H), 1.47-1.30 (m, 6H), 0.98 (t, $J = 7.0$ Hz, 3H); MS (ESI) m/z 358.4 [M+H]$^+$. 
**4-((6-(Diethylamino)hexyl)oxy)benzaldehyde (5o)**

Intermediate 4e was treated with diethylamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (2:1, v/v) as elution solvent to obtain the desired product 5o as a light yellow oil, yield 80.2%. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.88 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 4.10 (t, $J = 6.5$ Hz, 2H), 2.44 (q, $J = 6.5$ Hz, 4H), 2.35 (t, $J = 7.0$ Hz, 2H), 1.77-1.73 (m, 2H), 1.44-1.33 (m, 6H), 0.94 (t, $J = 7.0$ Hz, 6H); MS (ESI) $m/z$ 278.3 $[\text{M+H}]^+$. 

**4-((6-(Dimethylamino)hexyl)oxy)benzaldehyde (5p)**

Intermediate 4e was treated with dimethylamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (2:1, v/v) as elution solvent to obtain the desired product 5p as a light yellow oil, yield 80.5%. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.88 (s, 1H), 7.86 (d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 4.10 (t, $J = 6.5$ Hz, 2H), 2.19 (t, $J = 6.5$ Hz, 2H), 2.11 (s, 6H), 1.76-1.74 (m, 2H), 1.47-1.25 (m, 6H); MS (ESI) $m/z$ 250.2 $[\text{M+H}]^+$. 

**4-((6-(Dipropylamino)hexyl)oxy)benzaldehyde (5q)**

Intermediate 4e was treated with dipropylamine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (3:1, v/v) as elution solvent to obtain the desired product 5q as a light yellow oil, yield 79.6%. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.88 (s, 1H), 7.88 (d, $J = 8.5$ Hz, 2H), 7.13 (d, $J = 8.5$ Hz, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 2.34 (t, $J = 6.0$ Hz, 2H); MS (ESI) $m/z$ 241.2 $[\text{M+H}]^+$. 


**4-((6-(Pyrrolidin-1-yl)hexyl)oxy)benzaldehyde (5r)**

Intermediate 4e was treated with pyrrolidine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum CH₂Cl₂/MeOH (20:1, v/v) as elution solvent to obtain the desired product 5r as a pale yellow oil, yield 79.6%. ¹H NMR (500 MHz, DMSO-d₆) δ 9.88 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H), 2.60-2.54 (br s, 6H), 1.79-1.73 (m, 6H), 1.54-1.34 (m, 6H); MS (ESI) m/z 276.2 [M+H]+.

**4-((6-(Piperidin-1-yl)hexyl)oxy)benzaldehyde (5s)**

Intermediate 4e was treated with piperidine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (3:1, v/v) as elution solvent to obtain the desired product 5s as a pale yellow oil, yield 77.4%. ¹H NMR (500 MHz, DMSO-d₆) δ 9.88 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H), 2.29 (br s, 4H), 2.21 (t, J = 7.0 Hz, 2H), 1.77-1.72 (m, 2H), 1.50-1.30 (m, 12H); MS (ESI) m/z 290.3 [M+H]+.

**4-((6-(2-Methylpiperidin-1-yl)hexyl)oxy)benzaldehyde (5t)**

Intermediate 4e was treated with 2-methylpiperidine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (2:1, v/v) as elution solvent to obtain the desired product 5t as a light yellow oil, yield 77.4%. ¹H NMR (500 MHz, DMSO-d₆) δ 9.88 (s, 1H), 7.87 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 4.10 (t, J = 6.5 Hz, 2H), 2.04 (t, J = 7.0 Hz, 2H), 1.78-1.72 (m, 2H), 1.50-1.30 (m, 12H); MS (ESI) m/z 306.3 [M+H]+.
Hz, 2H), 2.77-2.73 (m, 1H), 2.61-2.56 (m, 1H), 2.23-2.17 (m, 2H), 2.07-2.02 (m, 1H), 1.75 (m, 2H), 1.60-1.16 (m, 12H), 0.98 (d, \( J = 6.5 \) Hz, 3H) ; MS (ESI) \( m/z \) 304.3 \([\text{M+H}]^+\).

4-((6-(4-Hydroxypiperidin-1-yl)hexyl)oxy)benzaldehyde (5u)

Intermediate 4e was treated with piperidin-4-ol according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with CH\(_2\)Cl\(_2\)/MeOH (10:1, v/v) as elution solvent to obtain the desired product 5u as a light yellow oil, yield 75.0%. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 9.89 (s, 1H), 7.88 (d, \( J = 8.5 \) Hz, 2H), 7.14 (d, \( J = 8.5 \) Hz, 2H), 4.11 (t, \( J = 6.5 \) Hz, 2H), 3.64-3.07 (m, 8H), 1.83-1.74 (m, 4H), 1.59 (br s, 4H), 1.50-1.44 (m, 2H), 1.39-1.34 (m, 2H); MS (ESI) \( m/z \) 306.3 \([\text{M+H}]^+\).

4-((6-Morpholinohexyl)oxy)benzaldehyde (5v)

Intermediate 4e was treated with morpholine according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (3:1, v/v) as elution solvent to obtain the desired product 5v as a light yellow oil, yield 73.1%. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \( \delta \) 9.88 (s, 1H), 7.87 (d, \( J = 8.5 \) Hz, 2H), 7.13 (d, \( J = 8.5 \) Hz, 2H), 4.10 (t, \( J = 6.5 \) Hz, 2H), 3.64-3.07 (m, 8H), 2.33 (br s, 4H), 2.26 (t, \( J = 7.5 \) Hz, 2H), 1.78-1.72 (m, 2H), 1.50-1.41(m, 4H), 1.38-1.32(m, 2H); MS (ESI) \( m/z \) 292.3 \([\text{M+H}]^+\).

General procedures for the preparation of (6a-v)

After the mixture of compound 3 (0.5 mmol) and sodium methylate (0.16 g, 3 mmol) in dry DMF were stirred at 0 °C for 30 min under argon, compounds 5a-v (0.45 mmol)
in dry DMF was added respectively. The resulting mixture was stirred overnight at room temperature, quenched by the addition of ice water and extracted by EtOAc. The solvent was removed and the crude product was purified by silica gel column chromatography.

\((E)-N\text{-}benzyl\text{-}2\text{-}(4\text{-}(3,5\text{-}dimethoxystyryl)phenoxy)\text{-}N\text{-}methylethanamine (6a)\)

Intermediate 5a was reacted with \(3\) according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (5:1, v/v) as elution solvent to obtain the desired product 6a as a light yellow oil, yield 50.2%; IR (KBr) \(\nu \text{ cm}^{-1}: 3454, 2936, 2836, 1595, 1510, 1457, 1250, 1204, 1152, 1065, 832, 739, 700; {^1H} \text{NMR (500 MHz, DMSO-d}_6) \delta 7.54 (d, J = 8.5 Hz, 2H, Ar-H), 7.37 (m, 4H, Ar-H), 7.29-7.26 (m, 1H, Ar-H), 7.23 (d, J = 16.5 Hz, 1H, CH=CH), 7.04 (d, J = 16.5 Hz, 1H, CH=CH), 6.97 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.5 Hz, 1H, Ar-H), 4.14 (t, J = 6.0 Hz, 2H, OCH\(_2\)), 3.79 (s, 6H, OCH\(_3\)), 3.60 (s, 2H, Ph-CH\(_2\)N), 2.77 (t, J = 6.0 Hz, 2H, NCH\(_2\)), 2.26 (s, 3H, NCH\(_3\)); {^{13}C} \text{NMR (125 MHz, DMSO-d}_6) \delta 161.17, 158.79, 139.95, 139.54, 130.07, 129.18, 129.08, 128.60, 128.31, 127.33, 126.69, 115.27, 104.74, 100.04, 66.55, 62.19, 55.77, 55.69, 42.89; Purity: 98.6% by HPLC (\(t_R 8.9 \text{ min}\)); MS (ESI) \(m/z\) 404.3 [M+H]\(^+\); HRMS (ESI) \(m/z\) 404.2221 [M+H]\(^+\) (calcd for C\(_{26}\)H\(_{30}\)NO\(_3\), 404.2220).

\((E)-N\text{-}benzyl\text{-}3\text{-}(4\text{-}(3,5\text{-}dimethoxystyryl)phenoxy)\text{-}N\text{-}methylpropan-1-amine (6b)\)

Intermediate 5b was reacted with \(3\) according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (30:1, v/v) as elution solvent to obtain the desired product 6b as a light
yellow oil, yield 48.3%; IR (KBr) ν 3454, 2953, 2837, 1560, 1511, 1459, 1251, 1204, 1153, 1065, 833, 738, 700 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.54 (d, J = 9.0 Hz, 2H, Ar-H), 7.32-7.31 (m, 4H, Ar-H), 7.27-7.21 (m, 2H, Ar-H, CH=CH), 7.04 (d, J = 16.0 Hz, 1H, CH=CH), 6.93 (d, J = 9.0 Hz, 2H, Ar-H), 6.76 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.5 Hz, 1H, Ar-H), 4.06 (t, J = 6.0 Hz, 2H, OCH₂), 3.80 (s, 6H, OCH₃), 3.50 (s, 2H, Ph-CH₂N), 2.51 (t, J = 7.0 Hz, 2H, NCH₂), 2.16 (s, 3H, NCH₃), 1.95-1.90 (m, 2H, alkyl chains-H); ¹³C NMR (125 MHz, DMSO-d₆) δ 161.17, 158.98, 139.97, 139.63, 129.97, 129.11, 128.56, 128.31, 127.24, 126.64, 115.23, 104.73, 100.02, 66.33, 62.07, 55.69, 53.78, 42.34, 27.20; Purity: 97.9% by HPLC (tᵣ 9.2 min); MS (ESI) m/z 418.3 [M+H]+; HRMS (ESI) m/z 418.2379 [M+H]+ (calcd for C₂₇H₃₂NO₃, 418.2377).

(E)-N-benzyl-4-(4-(3,5-dimethoxystyryl)phenoxy)-N-methylbutan-1-amine (6c)

Intermediate 5c was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (7:1, v/v) as elution solvent to obtain the desired product 6c as a colorless oil, yield 50.0%; IR (KBr) ν 3443, 2939, 2837, 1570, 1511, 1460, 1251, 1205, 1154, 1065, 833, 739, 700 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.35-7.30 (m, 4H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 7.23 (d, J = 16.0 Hz, 1H, CH=CH), 7.04 (d, J = 16.0 Hz, 1H, CH=CH), 6.94 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.80 (s, 6H, OCH₃), 3.47 (s, 2H, Ph-CH₂N), 2.40 (t, J = 7.0 Hz, 2H, NCH₂), 2.13 (s, 3H, NCH₃), 1.79-1.73 (m, 2H, alkyl chains-H), 1.66-1.60 (m, 2H,
alkyl chains-H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.17, 158.98, 139.97, 129.15, 129.12, 128.57, 128.30, 126.62, 115.23, 104.73, 100.02, 67.89, 62.05, 56.77, 55.69, 42.22, 40.10, 26.99, 23.74; Purity: 98.9% by HPLC ($t_R$ 10.0 min); MS (ESI) $m/z$ 432.4 [M+H]$^+$; HRMS (ESI) $m/z$ 432.2534 [M+H]$^+$ (calcd for C$_{28}$H$_{34}$NO$_3$, 432.2533).

(E)-N-benzyl-5-(4-(3,5-dimethoxystyryl)phenoxy)-N-methylpentan-1-amine (6d)

Intermediate 5d was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (10:1, v/v) as elution solvent to obtain the desired product 6d as a dark yellow oil, yield 48.8%; IR (KBr) $\nu$ 3444, 2939, 2864, 2837, 1596, 1511, 1460, 1251, 1204, 1154, 1066, 834, 741, 700 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.53 ($d$, $J$ = 8.5 Hz, 2H, Ar-H), 7.35-7.29 (m, 4H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 7.22 ($d$, $J$ = 16.5 Hz, 1H, CH=CH), 7.03 ($d$, $J$ = 16.5 Hz, 1H, CH=CH), 6.95 ($d$, $J$ = 8.5 Hz, 2H, Ar-H), 6.76 ($d$, $J$ = 2.0 Hz, 2H, Ar-H), 6.41 ($t$, $J$ = 2.0 Hz, 1H, Ar-H), 4.00 ($t$, $J$ = 6.5 Hz, 2H, OCH$_2$), 3.80 (s, 6H, OCH$_3$), 3.46 (s, 2H, Ph-CH$_2$N), 2.35 ($t$, $J$ = 7.0 Hz, 2H, NCH$_2$), 2.12 (s, 3H, NCH$_3$), 1.77-1.69 (m, 2H, alkyl chains-H), 1.57-1.51 (m, 2H, alkyl chains-H), 1.48-1.41 (m, 2H, alkyl chains-H); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.17, 159.01, 139.97, 139.82, 129.11, 128.55, 128.31, 127.21, 126.60, 115.20, 104.72, 100.01, 68.02, 62.11, 57.13, 55.69, 42.31, 29.05, 26.98, 23.83; Purity: 99.0% by HPLC ($t_R$ 11.3 min); MS (ESI) $m/z$ 446.4 [M+H]$^+$; HRMS (ESI) $m/z$ 446.2691 [M+H]$^+$ (calcd for C$_{29}$H$_{36}$NO$_3$, 446.2690).

(E)-N-benzyl-6-(4-(3,5-dimethoxystyryl)phenoxy)-N-methylhexan-1-amine (6e)

Intermediate 5e was reacted with 3 according to the general procedure to give a crude
product. Then it was purified using silica gel chromatography with petroleum ether/acetone (8:1, v/v) as elution solvent to obtain the desired product 6e as a light yellow oil, yield 51.0%; IR (KBr) ν 3455, 2937, 2837, 1597, 1511, 1460, 1251, 1204, 1153, 1067, 834, 740, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) δ 7.53 (d, \(J = 9.0\) Hz, 2H, Ar-H), 7.34-7.29 (m, 4H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 7.22 (d, \(J = 16.5\) Hz, 1H, CH=CH), 7.03 (d, \(J = 16.5\) Hz, 1H, CH=CH), 6.95 (d, \(J = 9.0\) Hz, 2H, Ar-H), 6.76 (d, \(J = 2.0\) Hz, 2H, Ar-H), 6.41 (t, \(J = 2.0\) Hz, 1H, Ar-H), 3.99 (t, \(J = 6.5\) Hz, 2H, OCH\(_2\)), 3.80 (s, 6H, OCH\(_3\)), 3.45 (s, 2H, Ph-CH\(_2\)N), 2.33 (t, \(J = 7.0\) Hz, 2H, NCH\(_2\)), 2.11 (s, 3H, NCH\(_3\)), 1.77-1.69 (m, 2H, alkyl chains-H), 1.53-1.32 (m, 6H, alkyl chains-H); \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): δ 161.17, 159.00, 139.97, 129.93, 129.12, 128.55, 128.31, 127.20, 126.61, 115.20, 104.72, 100.02, 68.00, 62.13, 57.13, 55.69, 42.33, 29.17, 27.20, 27.02, 25.88; Purity: 98.1% by HPLC (t\(_R\) 8.0 min); MS (ESI) \(m/z\) 460.4 [M+H\(^+\)]; HRMS (ESI) \(m/z\) 460.2849 [M+H\(^+\)] (calcd for C\(_{30}\)H\(_{38}\)NO\(_3\), 460.2846).

\((E)\)-N-benzyl-7-(4-(3,5-dimethoxystyryl)phenoxy)-N-methylheptan-1-amine (6f)

Intermediate 5f was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (10:1, v/v) as elution solvent to obtain the desired product 6f as a light yellow oil, yield 40.0%; IR (KBr) ν 3455, 2937, 2854, 1597, 1511, 1460, 1251, 1204, 1153, 1067, 834, 740, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) δ 7.53 (d, \(J = 9.0\) Hz, 2H, Ar-H), 7.34-7.29 (m, 4H, Ar-H), 7.27-7.24 (m, 1H, Ar-H), 7.22 (d, \(J = 16.5\) Hz, 1H, CH=CH), 7.03 (d, \(J = 16.5\) Hz, 1H, CH=CH), 6.95 (d, \(J = 9.0\) Hz, 2H, Ar-H), 6.76 (d, \(J = 2.0\) Hz, 2H, Ar-H), 6.41 (t, \(J = 2.0\) Hz, 1H, Ar-H), 3.99 (t, \(J = 6.5\) Hz, 2H,
OCH₂), 3.80 (s, 6H, OCH₃), 3.45 (s, 2H, Ph-CH₂N), 2.30 (t, J = 7.0 Hz, 2H, NCH₂), 2.10 (s, 3H, NCH₃), 1.76-1.69 (m, 2H, alkyl chains-H), 1.52-1.28 (m, 8H, alkyl chains-H); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.01, 139.97, 139.85, 129.93, 129.11, 129.08, 128.53, 128.30, 127.18, 126.60, 115.20, 104.72, 100.01, 68.00, 62.14, 57.15, 55.68, 42.32, 40.09, 29.31, 29.23, 27.20, 27.14, 25.90; Purity: 99.0% by HPLC (tᵣ 9.3 min); MS (ESI) m/z 474.4 [M+H]⁺; HRMS (ESI) m/z 474.3003 [M+H]⁺ (calcd for C₃₁H₄₀NO₃, 474.3002).

**(E)-N-benzyl-8-(4-(3,5-dimethoxystyryl)phenoxy)-N-methyloctan-1-amine (6g)**

Intermediate 5g was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (15:1, v/v) as elution solvent to obtain the desired product 6g as a light yellow oil, yield 41.5%; IR (KBr) ν 3448, 2933, 2854, 1595, 1511, 1459, 1251, 1204, 1152, 10676, 833, 738, 700 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.34-7.28 (m, 4H, Ar-H), 7.26-7.22 (m, 1H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (br s, 1H, Ar-H), 3.99 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.44 (s, 2H, Ph-CH₂N), 2.30 (t, J = 7.0 Hz, 2H, NCH₂), 2.10 (s, 3H, NCH₃), 1.76-1.68 (m, 2H, alkyl chains-H), 1.50-1.23 (m, 10H, alkyl chains-H); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.01, 139.97, 139.85, 129.93, 129.10, 129.08, 128.53, 128.30, 127.18, 126.60, 115.19, 104.72, 100.01, 68.01, 62.14, 57.17, 55.68, 42.32, 40.09, 29.31, 29.23, 29.15, 27.22, 27.20, 25.96; Purity: 99.2% by HPLC (tᵣ 15.7 min); MS (ESI) m/z 488.5 [M+H]⁺; HRMS (ESI) m/z 488.3158 [M+H]⁺
Intermediate 5h was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (20:1, v/v) as elution solvent to obtain the desired product 6h as a colorless oil, yield 51.3%; IR (KBr) ν 3444, 2936, 2857, 1602, 1512, 1463, 1247, 1206, 1057, 823, 701 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 9.0 Hz, 2H, Ar-H), 7.32-7.29 (m, 4H, Ar-H), 7.27-7.22 (m, 2H, Ar-H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.94 (d, J = 9.0 Hz, 2H, Ar-H), 6.75 (d, J = 2.5 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 3.97 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.53 (s, 2H, Ph-CH₂N), 2.48-2.43 (m, 2H, NCH₂CH₃), 2.39 (t, J = 7.5 Hz, 2H, NCH₃), 1.71-1.69 (m, 3H, alkyl chains-H), 1.46-1.32 (m, 6H, alkyl chains-H), 0.99 (t, J = 7.0 Hz, 3H, CH₂CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.00, 140.59, 139.97, 129.93, 129.11, 128.93, 128.50, 128.31, 127.03, 126.61, 115.19, 104.72, 100.01, 67.98, 58.01, 55.69, 52.98, 47.27, 29.16, 27.05, 26.98, 25.85, 12.16; Purity: 99.2% by HPLC (tᵣ 13.9 min); MS (ESI) m/z 474.4 [M+H]^⁺; HRMS (ESI) m/z 474.3002 [M+H]^⁺ (calcd for C₃₁H₄₀NO₃, 474.3003).

*(E)*-6-(4-(3,5-Dimethoxystyrlyl)phenoxy)-N-ethyl-N-(3-methoxybenzyl)hexan-1-amine (6i)

Intermediate 5i was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6i as a
colorless oil, yield 51.4%; IR (KBr) ν 3445, 2936, 2858, 2836, 1596, 1510, 1462, 1250, 1152, 1066, 834, 755 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 9.0 Hz, 2H, Ar-H), 7.38-7.35 (m, 1H, Ar-H), 7.24-7.19 (m, 2H, Ar-H, CH=CH), 7.03 (d, J = 16.0 Hz, 1H, CH=CH), 6.97-6.90 (m, 4H, Ar-H), 6.76 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 3.97 (t, J = 6.0 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.78 (s, 3H, OCH₃), 3.52 (s, 2H, Ph-CH₂N), 2.48-2.44 (q, J = 7.0 Hz, 2H, NCH₂CH₃), 2.41 (t, J = 7.0 Hz, 2H, NCH₂), 1.74-1.68 (m, 2H, alkyl chains-H), 1.49-1.31 (m, 6H, alkyl chains-H), 0.99 (t, J = 7.0 Hz, 3H, CH₂CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.16, 158.99, 157.74, 139.96, 129.92, 129.80, 129.10, 128.29, 127.95, 126.59, 120.52, 115.18, 111.09, 104.72, 100.01, 67.99, 55.75, 55.68, 55.35, 51.35, 51.55, 47.69, 29.18, 27.15, 27.10, 25.87, 12.38; Purity: 98.0% by HPLC (tᵣ 14.5 min); MS (ESI) m/z 504.5 [M+H]⁺; HRMS (ESI) m/z [M+H]⁺ 504.3105 (calcd for C₃₂H₄₂NO₄, 504.3108).

(E)-6-(4-(3,5-Dimethoxystyryl)phenoxy)-N-ethyl-N-(3-methoxybenzyl)hexan-1-amine (6j)

Intermediate 5j was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6j as a colorless oil, yield 53.2%; IR (KBr) ν 3450, 2936, 2859, 2835, 1596, 1511, 1460, 1252, 1152, 1065, 834, 780, 693 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 9.0 Hz, 2H, Ar-H), 7.24-7.20 (m, 2H, Ar-H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.94 (d, J = 8.5 Hz, 2H, Ar-H), 6.90-6.75 (br s, 2H, Ar-H), 6.81-6.78 (m,
1H, Ar-H), 6.76 (d, $J = 2.0$ Hz, 2H, Ar-H), 6.41 (t, $J = 2.0$ Hz, 1H, Ar-H), 3.97 (t, $J = 6.5$ Hz, 2H, OCH$_2$), 3.79 (s, 6H, OCH$_3$), 3.74 (s, 3H, OCH$_3$), 3.50 (s, 2H, Ph-CH$_2$N), 2.48-2.43 (q, $J = 7.0$ Hz, 2H, NCH$_2$CH$_3$), 2.39 (t, $J = 7.0$ Hz, 2H, NCH$_2$), 1.71-1.69 (m, 2H, alkyl chains-H), 1.46-1.33 (m, 6H, alkyl chains-H), 0.99 (t, $J = 7.0$ Hz, 3H, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.17, 159.72, 159.00, 142.37, 139.97, 129.93, 129.50, 129.11, 128.30, 126.60, 121.09, 115.18, 114.36, 112.47, 104.72, 100.01, 67.98, 57.99, 55.69, 55.36, 53.00, 47.34, 29.18, 27.07, 26.98, 25.86, 12.18; Purity: 97.5% by HPLC (t$_R$ 14.2 min); MS (ESI) $m/z$ 504.5 [M+H]$^+$; HRMS (ESI) $m/z$ [M+H]$^+$ 504.3105 (calcd for C$_{32}$H$_{42}$NO$_4$, 504.3108).

$(E)$-6-(4-(3,5-Dimethoxystyrlyl)phenoxy)-N-ethyl-N-(4-methoxybenzyl)hexan-1-amine (6k)

Intermediate 5k was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6k as a colorless oil, yield 43.2%; IR (KBr) $\nu$ 3446, 2936, 2858, 2836, 1596, 1512, 1461, 1250, 1204, 1153, 1066, 833 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.53 (d, $J = 9.0$ Hz, 2H, Ar-H), 7.24-7.21 (m, 3H, Ar-H, CH=CH), 7.03 (d, $J = 16.5$ Hz, 1H, CH=CH), 6.94 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.88-6.85 (m, 2H, Ar-H), 6.75 (d, $J = 2.0$ Hz, 2H, Ar-H), 6.41 (t, $J = 2.0$ Hz, 1H, Ar-H), 3.97 (t, $J = 6.5$ Hz, 2H, OCH$_2$), 3.80 (s, 6H, OCH$_3$), 3.74 (s, 3H, OCH$_3$), 3.45 (s, 2H, Ph-CH$_2$N), 2.45-2.41 (q, $J = 7.0$ Hz, 2H, NCH$_2$CH$_3$), 2.37 (t, $J = 7.0$ Hz, 2H, NCH$_2$), 1.71-1.69 (m, 2H, alkyl chains-H), 1.45-1.31 (m, 6H, alkyl chains-H), 0.98 (t, $J = 7.0$ Hz, 3H, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, DMSO-$d_6$):
δ 161.17, 159.00, 158.54, 139.97, 132.25, 130.08, 129.93, 129.11, 128.31, 126.60, 115.19, 113.94, 104.72, 100.01, 67.98, 57.28, 55.69, 55.46, 52.72, 47.04, 29.17, 27.04, 26.93, 25.83, 12.13; Purity: 98.2% by HPLC (tR 13.6 min); MS (ESI) m/z 504.5 [M+H]+; HRMS (ESI) m/z [M+H]+ 504.3105 (calcd for C32H42NO4, 504.3108). \((E)-6-(4-(3,5-Dimethoxystyryl)phenoxy)-N-ethyl-N-(2-fluorobenzyl)hexan-1-amine (6l)\)

Intermediate 5l was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6l as a colorless oil, yield 50.0%; IR (KBr) ν 3450, 2936, 2859, 1595, 1511, 1458, 1251, 1204, 1152, 1067, 833, 758 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 9.0 Hz, 2H, Ar-H), 7.46-7.42 (m, 1H, Ar-H), 7.32-7.27 (m, 1H, Ar-H), 7.20 (d, J = 16.0 Hz, 1H, CH=CH), 7.19-7.12 (m, 2H, Ar-H), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.94 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 8.5 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 3.97 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.58 (s, 2H, Ph-CH₂N), 2.45-2.40 (q, J = 7.0 Hz, 2H, NCH₂CH₃), 2.41 (t, J = 7.0 Hz, 2H, NCH₂), 1.73-1.67 (m, 2H, alkyl chains-H), 1.49-1.30 (m, 6H, alkyl chains-H), 1.00 (t, J = 7.0 Hz, 3H, CH₂CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 162.22, 161.17, 160.28, 159.00, 139.97, 131.63, 131.59, 129.93, 129.11, 129.06, 128.30, 126.61, 124.53, 124.51, 115.18, 104.73, 100.01, 67.98, 55.59, 53.03, 50.61, 47.40, 29.16, 27.01, 25.82, 12.20; Purity: 97.9% by HPLC (tR 13.7 min); MS (ESI) m/z 492.4 [M+H]+; HRMS (ESI) m/z [M+H]+ 492.2912 (calcd for C₃₁H₄₀FNO₃, 492.2908).

\((E)-6-(4-(3,5-Dimethoxystyrly)phenoxy)-N-ethyl-N-(2-fluorobenzyl)hexan-1-\)
amine (6m)

Intermediate 5m was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6m as a colorless oil, yield 51.1%; IR (KBr) ν 3444, 2935, 2859, 1594, 1511, 1458, 1251, 1204, 1152, 1066, 831, 782, 685 cm⁻¹; ¹H NMR (500 MHz, DMSO-­d₆) δ 7.53 (d, J = 9.0 Hz, 2H, Ar-H), 7.37-7.33 (m, 1H, Ar-H), 7.22 (d, J = 16.0 Hz, 1H, CH=CH), 7.17-7.12 (m, 2H, Ar-H), 7.07-7.01 (m, 2H, Ar-H, CH=CH), 6.94 (d, J = 8.5 Hz, 2H, Ar-H), 6.76 (d, J = 2.5 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 3.97 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.55 (s, 2H, Ph-CH₂N), 2.45-2.40 (q, J = 7.0 Hz, 2H, NCH₂CH₃), 2.40 (t, J = 7.0 Hz, 2H, NCH₃); ¹³C NMR (125 MHz, DMSO-­d₆): δ 163.72, 161.79, 161.17, 158.99, 139.97, 130.40, 130.33, 129.93, 129.10, 128.30, 126.60, 124.76, 124.74, 115.18, 104.72, 100.01, 67.98, 57.44, 55.68, 53.09, 47.04, 29.16, 27.03, 26.98, 25.84, 12.16; Purity: 98.4% by HPLC (tR 13.9 min); MS (ESI) m/z 492.4 [M+H]^+; HRMS (ESI) m/z [M+H]^+ 492.2912 (calcd for C₃₁H₃₉FNO₃, 492.2908).

(E)-6-(4-(3,5-Dimethoxystyryl)phenoxy)-N-ethyl-N-(4-fluorobenzyl)hexan-1-amine (6n)

Intermediate 5n was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/EtOAc (30:1, v/v) as elution solvent to obtain the desired product 6n as a
colorless oil, yield 49.7%; IR (KBr) ν 3447, 2935, 2858, 1597, 1511, 1461, 1252, 1205, 1154, 1067, 833 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.51 (d, J = 9.0 Hz, 2H, Ar-H), 7.33-7.31 (dd, J = 6.0 Hz, 2.0 Hz, 2H, Ar-H), 7.20 (d, J = 16.5 Hz, 1H, CH=CH), 7.10 (t, J = 9.0 Hz, 2H, Ar-H), 7.01 (d, J = 16.5 Hz, 1H, CH=CH), 6.92 (d, J = 8.5 Hz, 2H, Ar-H), 6.73 (d, J = 2.5 Hz, 2H, Ar-H), 6.38 (t, J = 2.0 Hz, 1H, Ar-H), 3.95 (t, J = 6.5 Hz, 2H, OCH₂), 3.77 (s, 6H, OCH₃), 3.49 (s, 2H, Ph-CH₂N), 2.45-2.40 (q, J = 7.0 Hz, 2H, NCH₂CH₃), 2.36 (t, J = 7.0 Hz, 2H, NCH₂), 1.68-1.67 (m, 2H, alkyl chains-H), 1.42-1.30 (m, 6H, alkyl chains-H), 0.96 (t, J = 7.0 Hz, 3H, CH₂CH₃);
¹³C NMR (125 MHz, DMSO-d₆): δ 162.49, 161.16, 160.57, 158.98, 139.95, 136.71, 130.66, 130.60, 129.93, 129.09, 128.29, 126.60, 115.26, 115.18, 115.09, 104.72, 100.01, 67.98, 57.11, 55.68, 52.90, 47.19, 29.15, 27.03, 26.96, 25.84, 12.13; Purity: 98.9% by HPLC (tᵣ 13.9 min); MS (ESI) m/z 492.4 [M+H]+; HRMS (ESI) m/z [M+H]+ 492.2912 (calcd for C₃₁H₃₉FNO₃, 492.2908).

(⁵⁻)⁶-(4-(3,5-Dimethoxystyryl)phenoxy)-N,N-diethylhexan-1-amine (6o)

Intermediate 5o was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (9:1, v/v) as elution solvent to obtain the desired product 6o as a light yellow oil, yield 45.4%; IR (KBr) ν 3455, 2936, 2838, 1597, 1512, 1462, 1251, 1205, 1153, 1065, 836 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.47 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 2.49-2.40 (br s, 6H, NCH₂), 1.75-
1.71 (m, 2H, alkyl chains-H), 1.45-1.33 (m, 6H, alkyl chains-H), 0.97 (t, J = 7.5 Hz, 6H, CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.00, 139.97, 129.94, 129.10, 128.31, 126.61, 115.20, 104.72, 100.01, 67.99, 61.88, 55.68, 46.84, 29.19, 27.16, 25.92, 16.71; Purity: 98.9% by HPLC (tᵣ 11.1 min); MS (ESI) m/z 412.4 [M+H]⁺; HRMS (ESI) m/z 412.2847 [M+H]⁺ (calcd for C₂₆H₃₈NO₃, 384.2546).

**(E)-6-(4-(3,5-Dimethoxystyryl)phenoxy)-N,N-dimethylhexan-1-amine (6p)**

Intermediate 5p was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (8:1, v/v) as elution solvent to obtain the desired product 6p as a colorless oil, yield 51.0%; IR (KBr) ν 3450, 2933, 2856, 1597, 1512, 1462, 1384, 1251, 1205, 1154, 1066, 836, 683 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.0 Hz, 1H, CH=CH), 7.03 (d, J = 16.0 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 1.5 Hz, 2H, Ar-H), 6.40 (d, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.80 (s, 6H, OCH₃), 2.20 (t, J = 7.0 Hz, 2H, NCH₂), 2.12 (s, 6H, NCH₃), 1.77-1.68 (m, 2H, alkyl chains-H), 1.48-1.31 (m, 6H, alkyl chains-H); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.01, 139.97, 129.94, 129.11, 128.31, 126.61, 115.21, 104.72, 100.02, 68.00, 59.57, 55.69, 45.66, 29.19, 27.48, 27.11, 25.94; Purity: 99.1% by HPLC (tᵣ 10.7 min); MS (ESI) m/z 384.4 [M+H]⁺; HRMS (ESI) m/z 384.2531 [M+H]⁺ (calcd for C₂₄H₃₆NO₃, 384.2533).

**(E)-6-(4-(3,5-Dimethoxystyryl)phenoxy)-N,N-dipropylhexan-1-amine (6q)**

Intermediate 5q was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum
ether/acetone (15:1, v/v) as elution solvent to obtain the desired product 6q as a light yellow oil, yield 50.1%; IR (KBr) ν 3444, 2934, 2870, 1597, 1512, 1462, 1250, 1204, 1153, 1069, 835 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.40 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 2.33 (br s, 6H, NCH₂), 1.73-1.71 (m, 2H, alkyl chains-H), 1.45-1.35 (m, 10H, alkyl chains-H, CH₂CH₃), 0.85 (t, J = 7.5 Hz, 6H, CH₂CH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.00, 139.96, 129.93, 129.10, 128.30, 126.60, 115.18, 104.72, 100.01, 67.97, 56.06, 55.68, 53.95, 29.19, 27.08, 25.91, 20.43, 20.34, 12.26; Purity: 99.0% by HPLC (tᵣ 12.8 min); MS (ESI) m/z 440.4 [M+H]+; HRMS (ESI) m/z 440.3160 [M+H]+ (calcd for C₂₈H₄₂NO₃, 440.3159).

(E)-1-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)pyrrolidine (6r)

Intermediate 5r was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (5:1, v/v) as elution solvent to obtain the desired product 6r as a dark yellow oil, yield 47.7%; IR (KBr) ν 3444, 2935, 2858, 1596, 1512, 1460, 1251, 1204, 1153, 1067, 836, 685 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.40 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 2.41-2.36 (m, 6H, NCH₂), 1.76-1.67 (m, 6H, alkyl chains-H, CH₂CH₂), 1.48-1.35 (m, 6H, alkyl chains-H); ¹³C NMR
(125 MHz, DMSO-$d_6$): $\delta$ 161.20, 159.01, 139.97, 129.94, 129.11, 128.31, 126.61, 115.21, 104.72, 100.01, 68.01, 56.15, 55.69, 54.09, 29.17, 28.86, 27.30, 25.97, 23.58; Purity: 98.7% by HPLC ($t_R$ 11.0 min); MS (ESI) $m/z$ 410.4 [M+H]$^+$; HRMS (ESI) $m/z$ 410.2692 [M+H]$^+$ (calcd for C$_{26}$H$_{36}$NO$_3$, 410.2690).

(E)-1-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)piperidine (6s)

Intermediate 5s was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (8:1, v/v) as elution solvent to obtain the desired product 6s as a dark yellow oil, yield 46.0%; IR (KBr) $\nu$ 3449, 2920, 2851, 1600, 1512, 1464, 1385, 1251, 1205, 1155, 1065, 839, 690 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.53 (d, $J = 8.5$ Hz, 2H, Ar-H), 7.22 (d, $J = 16.5$ Hz, 1H, CH=CH), 7.03 (d, $J = 16.5$ Hz, 1H, CH=CH), 6.95 (d, $J = 8.5$ Hz, 2H, Ar-H), 6.75 (d, $J = 2.0$ Hz, 2H, Ar-H), 6.40 (t, $J = 2.0$ Hz, 1H, Ar-H), 3.99 (t, $J = 6.5$ Hz, 2H, OCH$_2$), 3.79 (s, 6H, OCH$_3$), 2.32-2.22 (m, 6H, NCH$_2$), 1.76-1.70 (m, 2H, alkyl chains-H), 1. 52-1.31 (m, 12H, alkyl chains-H, CH$_2$CH$_2$CH$_2$); $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 161.17, 159.01, 139.97, 129.93, 129.11, 128.31, 126.61, 115.21, 104.72, 100.01, 68.00, 59.06, 55.69, 54.57, 29.16, 27.26, 26.80, 26.06, 25.96, 24.66; Purity: 97.9% by HPLC ($t_R$ 6.2 min); MS (ESI) $m/z$ 424.4 [M+H]$^+$; HRMS (ESI) $m/z$ 424.2844 [M+H]$^+$ (calcd for C$_{27}$H$_{38}$NO$_3$, 424.2846).

(E)-1-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)-2-methylpiperidine (6t)

Intermediate 5t was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (6:1, v/v) as elution solvent to obtain the desired product 6t as a dark
yellow oil, yield 49.0%; IR (KBr) ν 3451, 2919, 2851, 1637, 1511, 1460, 1384, 1261, 1153, 1095, 802 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.94 (d, J = 9.0 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 2.78-2.76 (m, 1H, NCH), 2.63-2.57 (m, 1H, NCH), 2.23 (br s, 2H, NCH₂), 2.07 (br s, 1H, NCH), 1.75-1.72 (m, 2H, alkyl chains-H), 1.57-1.18 (m, 12H, alkyl chains-H, CH₂CH₂CH₂), 1.00 (t, J = 3.0 Hz, 3H, CHCH₃); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.00, 139.97, 129.93, 129.11, 128.31, 126.61, 115.20, 104.72, 100.01, 68.00, 55.74, 55.69, 55.72, 51.85, 34.66, 29.19, 27.29, 26.27, 25.94, 25.86, 23.94, 18.97; Purity: 99.2% by HPLC (tR 6.3 min); MS (ESI) m/z 438.4 [M+H]⁺; HRMS (ESI) m/z 438.3005 [M+H]⁺ (calcd for C₂₈H₄₀NO₃, 438.3003).

(E)-1-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)piperidin-4-ol (6u)

Intermediate 5u was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with CH₂Cl₂/MeOH (20:1, v/v) as elution solvent to obtain the desired product 6u as a colorless oil, yield 44.7%; IR (KBr) ν 3424, 2936, 2865, 1685, 1596, 1512, 1462, 1320, 1253, 1162, 1069, 836, 798, 684 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.5 Hz, 1H, CH=CH), 7.03 (d, J = 16.5 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 4.52 (d, J = 3.5 Hz, 1H, OH), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.43 (br s, 1H, CHOH), 2.69 (m, 2H, NCH₂), 2.25 (br s, 2H, NCH₂), 1.98 (br s, 2H,
NCH₂), 1.75-1.70 (m, 4H, alkyl chains-H, CH₂CH₂), 1.47-1.31 (m, 8H, alkyl chains-H, CH₂CH₂); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 159.01, 139.97, 129.94, 129.11, 128.31, 126.61, 115.21, 104.73, 100.02, 68.01, 58.31, 55.69, 51.56, 34.93, 29.16, 27.25, 27.08, 25.94; Purity: 98.1% by HPLC (0-20 min, H₂O (tᵣ 10.6 min); MS (ESI) m/z 440.4 [M+H]⁺; HRMS (ESI) m/z 440.2796 [M+H]⁺ (calcd for C₂₇H₃₈NO₄, 440.2795).

(E)-4-(6-(4-(3,5-Dimethoxystyryl)phenoxy)hexyl)morpholine (6v)

Intermediate 5v was reacted with 3 according to the general procedure to give a crude product. Then it was purified using silica gel chromatography with petroleum ether/acetone (10:1, v/v) as elution solvent to obtain the desired product 6v as a light yellow oil, yield 48.2%; IR (KBr) ν 3457, 2937, 2858, 1597, 1512, 1462, 1251, 1205, 1154, 1064, 836, 686 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.53 (d, J = 8.5 Hz, 2H, Ar-H), 7.22 (d, J = 16.0 Hz, 1H, CH=CH), 7.03 (d, J = 16.0 Hz, 1H, CH=CH), 6.95 (d, J = 8.5 Hz, 2H, Ar-H), 6.75 (d, J = 2.0 Hz, 2H, Ar-H), 6.41 (t, J = 2.0 Hz, 1H, Ar-H), 4.00 (t, J = 6.5 Hz, 2H, OCH₂), 3.79 (s, 6H, OCH₃), 3.57 (t, J = 3.5 Hz, 4H, OCH₂), 2.34 (br s, 4H, NCH₂), 2.27 (t, J = 7.0 Hz, 2H, NCH₂), 1.76-1.70 (m, 2H, alkyl chains-H), 1.49-1.41 (m, 4H, alkyl chains-H), 1.38-1.31 (m, 2H, alkyl chains-H); ¹³C NMR (125 MHz, DMSO-d₆): δ 161.17, 158.00, 139.96, 129.94, 129.10, 128.31, 126.61, 115.21, 104.72, 100.01, 67.99, 66.71, 58.74, 55.69, 53.90, 29.15, 27.13, 26.38, 25.93; Purity: 98.2% by HPLC (tᵣ 9.8 min); MS (ESI) m/z 426.3 [M+H]⁺; HRMS (ESI) m/z 426.2640 [M+H]⁺ (calcd for C₂₆H₃₆NO₄, 426.2639).

In vitro inhibition of AChE and BuChE
Acetylcholinesterase (AChE, E.C. 3.1.1.7, from the electric eel), butyrylcholinesterase (BuChE, E.C. 3.1.1.8, from equine serum), 5,5’-dithiobis-(2-nitrobenzoic acid) (Ellman’s reagent, DTNB), acetylthiocholine chloride (ATC), and butylthiocholine chloride (BTC) were purchased from Sigma-Aldrich. The capacity of the test compounds to inhibit AChE and BuChE activities was assessed by Ellman’s method. Test compounds were dissolved in a minimum volume of DMSO (1%) and were diluted using the buffer solution (50 mM Tris-HCl, pH = 8.0, 0.1 M NaCl, 0.02 M MgCl$_2$·6H$_2$O) to the final concentration. In 96-well plates, 160 μL of 1.5 mM DTNB and 50 μL of AChE (0.22 U/mL prepared in 50 mM Tris-HCl, pH = 8.0, 0.1% w/v bovine serum albumin (BSA)) or 50 μL of BuChE (0.12 U/mL prepared in 50 mM Tris-HCl, pH = 8.0, 0.1% w/v BSA) were incubated with 10 μL of various concentrations of test compounds (0.001–100 μM) at 37 °C for 6 min followed by the addition of 30 μL acetylthiocholine iodide (15 mM) or S-butyrylthiocholine iodide (15 mM) and the absorbance was measured at different time intervals (0, 60, 120, and 180 s) at a wavelength of 405 nm. The concentration of compound producing 50% of enzyme activity inhibition (IC$_{50}$) was calculated by nonlinear regression analysis of the response-concentration (log) curve, using a Specta Max Plus 384 multidetection microplate reader (Molecular Devices, Sunnyvale, CA). Calculations were performed according to the method of Ellman et al. Results are expressed as the mean ± SEM of at least three different experiments performed in triplicate.

**Kinetic characterization of AChE inhibition**

To obtain the mechanism of action of 6h, reciprocal plots of 1/velocity versus
1/[substrate] were constructed at different concentrations of the substrate thiocholine iodide (0.05–0.5 mM) by using Ellman’s method. Compound 6h was added to the assay solution and pre-incubated with the enzyme at 37 °C for 15 min, followed by the addition of ATC. The assay solution (200 µL) containing compound 6h (0.40, 0.80, 1.60 µM), DTNB (1.5 mM), 10 µL AChE and ATCI (0.05, 0.075, 0.1, 0.15, 0.2, 0.5 mM) was dissolved in 0.1 M KH$_2$PO$_4$/K$_2$HPO$_4$ buffer (pH 8.0). Kinetic characterization of the hydrolysis of acetylthiocholine catalyzed by AChE was done spectrometrically at 405 nm. A parallel control experiment was carried out without compound 6h in the mixture. Slopes of these reciprocal plots were then plotted against the concentration of 6h in a weighted analysis and $K_i$ was determined as the intercept on the negative x-axis. Data analysis was performed with GraphPad Prism 4.03 software (GraphPad Software Inc.).

**Molecular docking study**

All calculations and analyses were carried out with Molecular Operating Environment (MOE) program (Chemical Computing Group, Montreal, Canada). The X-ray crystal structure of the AChE complex with bis(7)–tacrine (PDB ID: 2CKM) was applied to build the starting model of AChE, which was obtained from the Protein Data Bank (www.rcsb.org). Heteroatoms and water molecules in the PDB files were removed and all hydrogen atoms were subsequently added to the proteins. Compound 6h was drawn in MOE. The compound was then protonated using the protonate 3D protocol and energy was minimized using the MMFF94x force field in MOE. After the enzymes and compound 6h were ready for the docking study, 6h was docked into the
active site of the protein by the “Triangle Matcher” method. The Dock scoring in MOE software was done using ASE scoring function and Forcefield was selected as the refinement method. The best 10 poses of molecules were retained and scored. After docking, the geometry of resulting complex was studied using the MOE’s pose viewer utility.

**Inhibition of Aβ_42 self-induced aggregation**

Inhibition of Aβ_42 aggregation was measured using a Thioflavon T(ThT)-binding assay. Resveratrol and curcumin were used as reference compounds. HFIP pretreated Aβ_42 samples (Anaspec Inc) were resolubilized with a 50 mM phosphate buffer (pH 7.4) to give a 25 μM solution. Each test compound was firstly prepared in DMSO at a concentration of 10 mM and then 1 μL of each was added to the well of black, opaque Corning 96-well plates such that the final solvent concentration was 10%. The final concentration of each compound was 20 μM, which was prepared in independent triplicates. The solvent control was also included. Then, 9 μL of 25 μM Aβ_42 sample was added to each well and the samples mixed by gentle trapping. Plates were covered to minimize evaporation and incubated in dark at room temperature for 46-48 h with no agitation. After the incubation period, 200 μL of 5 μM ThT in 50 mM glycine-NaOH buffer (pH 8.0) was added to each well. Fluorescence was measured on a SpectraMax M5 muti-mode plate reader (Molecular Devices, Sunnyvale, CA, USA) with excitation and emission wavelengths of 446 nm and 490 nm, respectively. The fluorescence intensities were compared and the percent inhibition due to the presence of the inhibitor was calculated by the following formula: 100 – (IFi/IFo ×
100), where IFi and IFo are the fluorescence intensities obtained for Aβ plus AChE in the presence and in the absence of inhibitor, respectively, minus the fluorescence intensities due to the respective blanks.

**In vitro inhibition of Monoamine oxidase**

Human MAO-A and MAO-B were purchased from Sigma-Aldrich. The capacity of the test compounds to inhibit MAO-A and MAO-B activities was assessed by Amplex Red MAO assay. Briefly, 0.1 mL of sodium phosphate buffer (0.05 M, pH 7.4) containing the test drugs at various concentrations and adequate amounts of recombinant hMAO-A or hMAO-B required and adjusted to obtain in our experimental conditions the same reaction velocity, i.e., to oxidize (in the control group) the same concentration of substrate: 165 pmol of p-tyramine/min (hMAO-A: 1.1 μg protein; specific activity: 150nmol of p-tyramine oxidized to p-hydroxyphenylacetaldehyde/min/mg protein; hMAO-B: 7.5 μg protein; specific activity: 22 nmol of p-tyramine transformed/min/mg protein) were incubated for 15 min at 37 °C in a flat-black-bottom 96-well microtest plate placed in a dark fluorimeter chamber. After this incubation period, the reaction was started by adding 200 μM (final concentrations) Amplex Red reagent, 1 U/mL horseradish peroxidase, and 1 mM p-tyramine. The production of H$_2$O$_2$ and consequently, of resorufin, was quantified at 37 °C in a SpectraMax Paradigm (Molecular Devices, Sunnyvale, CA) muti-mode detection platform reader based on the fluorescence generated (excitation, 545 nm; emission, 590 nm). The specific fluorescence emission was calculated after subtraction of the background activity. The background activity was determined from
wells containing all components except the hMAO isoforms, which were replaced by a sodium phosphate buffer solution (0.05 M, pH 7.4). The percent inhibition was calculated by the following expression: $(1 - \frac{IF_i}{IF_c}) \times 100$ in which $IF_i$ and $IF_c$ are the fluorescence intensities obtained for hMAO in the presence and absence of inhibitors after subtracting the respective background.

**SH-SY5Y neuroblastoma cell toxicity**

The toxicity effect of test compound on the human neuroblastoma cell line SH-SY5Y cells was examined according to the previous methods. The SH-SY5Y cells were cultured in Eagle’s minimum essential medium (EMEM)/ham’s F-12 (1:1) medium supplemented with 10% fetal bovine serum (FBS), 100 U/mL penicillin and 100 μg/mL streptomycin, at 37 °C in a humidified atmosphere containing 5% CO$_2$. Cells were subcultured in 96-well plates at a seeding density of 10,000 cells per well and allowed to adhere and grow. When cells reached the required confluence, they were placed into serum-free medium and treated with compound 6r. Twenty-four hours later the survival of cells was determined by MTT assay. Briefly, after incubation with 20 μL of MTT at 37 °C for 4 h, living cells containing MTT formazan crystals were solubilized in 200 μL DMSO. The absorbance of each well was measured using a microculture plate reader with a test wavelength of 570 nm and a reference wavelength of 630 nm. Results are expressed as the mean ± SD of three independent experiments.