Supplementary materials

Synthesis and Pharmacological Evaluation of Multi-Functional Homoisoflavonoid Derivatives as Potent Inhibitors of Monoamine Oxidase B and Cholinesterase for the Treatment of Alzheimer’s disease

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1. Experimental section

Chemistry

Reagents and solvents were purchased from common commercial suppliers and were used without further purification. Reaction progress was monitored using analytical thin layer chromatography (TLC) on precoated silica gel GF254 (Qingdao Haiyang Chemical Plant, Qingdao, China) plates and the spots were detected under UV light (254 nm or 365 nm). IR (KBr-disc) spectra were recorded by Bruker Tensor 27 spectrometer. Melting points (uncorrected) were determined with an XT-4 micromelting point instrument. $^1$H and $^{13}$C NMR spectra were recorded in CDCl$_3$ or DMSO-$d_6$ solutions using a Bruker ACF-500 spectrometer at 25 °C. Mass spectra were obtained on a Mariner ESI-TOF spectrometer (HRESIMS). The purity of target compounds was determined by HPLC (Agilent 1100 infinity HPLC system). Column chromatography was performed on silica gel (90-150 μm; Qingdao Marine Chemical Inc.).

General procedures for the preparation of 5-7.

A mixture of chroman-4-one (1.0mmol), substituted benzaldehyde (1.0mmol), and piperidine (1ml) in ethanol (20ml) was stirred at room temperature. The reaction mixture was regularly monitored for reaction progress by TLC using petroleum ether and ethyl acetate (3:1) as the solvent system. The reaction was generally complete in 12 h, the solvent was removed under reduced pressure. The residue was chromatographed over silica gel column using mixtures of petroleum ether and ethyl acetate (10:1) as eluent to give 5-7 (32-54% yield).
(E)-3-(4-hydroxybenzylidene)chroman-4-one (5). Yield: 45%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.15 (s, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.70 (s, 1H), 7.61 – 7.58 (m, 1H), 7.36 (d, $J = 8.5$ Hz, 2H), 7.15 – 7.12 (m, 1H), 7.06 (d, $J = 8.3$ Hz, 1H), 6.91 (d, $J = 8.5$ Hz, 2H), 5.45 (d, $J = 1.4$ Hz, 2H).

(E)-3-(2-hydroxybenzylidene)chroman-4-one (6). Yield: 32%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 10.19 (s, 1H), 7.91 (d, $J = 8.0$ Hz, 1H), 7.89 (s, 1H), 7.61 (t, $J = 7.7$ Hz, 1H), 7.32 (t, $J = 7.7$ Hz, 1H), 7.15 (t, $J = 7.4$ Hz, 2H), 7.07 (d, $J = 8.3$ Hz, 1H), 6.98 (d, $J = 8.2$ Hz, 1H), 6.92 (t, $J = 7.4$ Hz, 1H), 5.34 (s, 2H).

(E)-3-(3-hydroxybenzylidene)chroman-4-one (7). Yield: 54%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 9.74 (s, 1H), 7.91 (d, $J = 7.8$ Hz, 1H), 7.69 (s, 1H), 7.62 (t, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 7.16 (t, $J = 7.5$ Hz, 1H), 7.08 (d, $J = 8.3$ Hz, 1H), 6.89 (d, $J = 8.0$ Hz, 2H), 6.85 (s, 1H), 5.43 (d, $J = 1.9$ Hz, 2H).

**General procedure for the preparation of (8-15).**

A mixture of an appropriate amount of 5-7 (1 mmol) and K$_2$CO$_3$ (2 mmol), different available α,ω-dibromoalkanes (5mmol) in acetonitrile (10 ml) were heated at 65°C for 8 h. After cooling to room temperature, the mixtures were filtered and the filtrates were evaporated under vacuum. The crude solid was purified by silica gel chromatography with petroleum ether/ethyl acetate (60:1).

(E)-3-(4-(2-bromoethoxy)benzylidene)chroman-4-one (8). Yield: 47%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.7$ Hz, 1H), 7.75 (s, 1H), 7.64 – 7.58 (m, 1H), 7.47 (d, $J = 8.6$ Hz, 2H), 7.17 – 7.14 (m, 1H), 7.12 (d, $J = 8.6$ Hz, 2H), 7.08 (d, $J = 8.3$ Hz, 1H), 5.46 (d, $J = 2.0$ Hz, 2H), 4.44 (t, $J = 5.4$ Hz, 2H), 3.86 (t, $J = 5.4$ Hz, 2H).
(E)-3-(4-(3-bromopropoxy)benzylidene)chroman-4-one (9). Yield: 40%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.8$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.47 (d, $J = 8.7$ Hz, 2H), 7.16 – 7.13 (m, 1H), 7.11 (d, $J = 8.7$ Hz, 2H), 7.08 (d, $J = 8.3$ Hz, 1H), 5.46 (d, $J = 1.5$ Hz, 2H), 4.19 (t, $J = 6.0$ Hz, 2H), 3.71 (t, $J = 6.6$ Hz, 2H), 2.33-2.28 (m, 2H).

(E)-3-(4-(4-bromobutoxy)benzylidene)chroman-4-one (10). Yield: 43%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.46 (d, $J = 8.7$ Hz, 2H), 7.16 – 7.13 (m, 1H), 7.08 (d, $J = 8.7$ Hz, 2H), 7.07 (d, $J = 8.3$ Hz, 1H), 5.46 (d, $J = 1.7$ Hz, 2H), 4.11 (t, $J = 6.3$ Hz, 2H), 3.64 (t, $J = 6.7$ Hz, 2H), 2.03 – 1.97 (m, 2H), 1.91 – 1.86 (m, 2H).

(E)-3-(4-((6-bromohexyl)oxy)benzylidene)chroman-4-one (11). Yield: 41%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J = 8.5$ Hz, 2H), 7.16 – 7.13 (m, 1H), 7.07 (d, $J = 8.4$ Hz, 3H), 5.46 (s, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 3.57 (t, $J = 6.6$ Hz, 2H), 1.89 – 1.82 (m, 2H), 1.80 – 1.73 (m, 2H), 1.50 – 1.45 (m, 4H).

(E)-3-(2-(2-bromoethoxy)benzylidene)chroman-4-one (12). Yield: 40%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.93 (s, 1H), 7.91 (d, $J = 7.9$ Hz, 1H), 7.64 – 7.64 (m, 1H), 7.53 – 7.46 (m, 2H), 7.16 (t, $J = 6.5$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 5.33 (d, $J = 1.9$ Hz, 2H), 4.45 – 4.43 (m, 2H), 3.8 – 3.84 (m, 2H).

(E)-3-(2-(3-bromopropoxy)benzylidene)chroman-4-one (13). Yield: 42%, yellow solid. $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.91 (d, $J = 7.9$ Hz, 1H), 7.88 (s, 1H), 7.64 – 7.60 (m, 1H), 7.51 – 7.46 (m, 1H), 7.22 (d, $J = 6.2$ Hz, 1H), 7.19 (d, $J = 8.3$ Hz, 1H), 7.15 (d, $J = 7.5$ Hz, 1H), 7.08 (t, $J = 7.5$ Hz, 2H), 5.32 (d, $J = 1.9$ Hz, 2H), 4.20 (t, $J = 6.0$ Hz, 2H), 3.67 (t, $J = 6.5$ Hz, 2H), 2.33 – 2.28 (m, 2H).
(\textit{E})-3-(3-(2-bromoethoxy)benzylidene)chroman-4-one (14). Yield: 45\%, yellow solid. \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta\) 7.91 (d, \(J = 7.9\) Hz, 1H), 7.76 (s, 1H), 7.65 – 7.61 (m, 1H), 7.46 – 7.43 (m, 1H), 7.18 – 7.15 (m, 1H), 7.12 – 7.05 (m, 4H), 5.45 (d, \(J = 1.9\) Hz, 2H), 4.42 (t, \(J = 5.4\) Hz, 2H), 3.85 (t, \(J = 5.5\) Hz, 2H).

(\textit{E})-3-(3-(3-bromopropoxy)benzylidene)chroman-4-one (15). Yield: 40\%, yellow solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.03 (d, \(J = 7.9\) Hz, 1H), 7.84 (s, 1H), 7.52 – 7.48 (m, 1H), 7.38 – 7.35 (m, 1H), 7.09 – 7.06 (m, 1H), 7.00 – 6.94 (m, 2H), 6.90 (d, \(J = 7.6\) Hz, 1H), 6.85 (s, 1H), 5.35 (d, \(J = 1.8\) Hz, 2H), 4.14 (t, \(J = 5.8\) Hz, 2H), 3.62 (t, \(J = 6.4\) Hz, 2H), 2.34 (p, \(J = 6.1\) Hz, 2H).

General procedure for the preparation of compounds 16-45.

A mixture of 8-15 (1 mmol) and K\textsubscript{2}CO\textsubscript{3} (4 mmol), different available secondary amines (4 mmol) in acetonitrile (6 ml).\textsuperscript{3} The reaction mixture was heated at 65\(^\circ\)C for 12 h, cooled to room temperature. The mixture was filtered and the solvent was removed under reduced pressure. The obtained crude solid was purified by silica gel chromatography with CH\textsubscript{2}Cl\textsubscript{2}/MeOH/Et\textsubscript{3}N (50:1:0.05-100:1:0.1) or petroleum ether/ethyl acetate (10:1) to give the desired product 16-45.

(E)-3-(4-(2-(dimethylamino)ethoxy)benzylidene)chroman-4-one (16). Yield 49\%, bright yellow solid; mp 91–93 \(^\circ\)C; IR (KBr) \(\nu\) 3435, 2945, 1662, 1605, 1513, 1480, 1327, 1309, 1254, 1182, 1156, 1021, 959, 827, 779, 755 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (500 MHz, DMSO-\textit{d}_6) \(\delta\) 7.85 (d, \(J = 7.8\) Hz, 1H), 7.70 (s, 1H), 7.58 – 7.55 (m, 1H), 7.42 (d, \(J = 8.8\) Hz, 2H), 7.12 – 7.08 (m, 1H), 7.05 (d, \(J = 8.8\) Hz, 2H), 7.03 (d, \(J = 7.4\) Hz, 1H), 5.41 (d, \(J = 1.9\) Hz, 2H), 4.14 (t, \(J = 5.7\) Hz, 2H), 2.74 (t, \(J = 5.7\) Hz, 2H), 2.29 (s, 6H). \textsuperscript{13}C NMR (125 MHz, DMSO-\textit{d}_6) \(\delta\) 181.52, 160.97, 160.14, 136.94, 136.54, 132.99, 129.07, 127.69, 126.87, 122.40, 122.06, 118.34, 115.36, 67.99, 65.97, 57.74, 55

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(E)-3-(4-(3-(dimethylamino)propoxy)benzylidene)chroman-4-one (17). Yield 40%, canary yellow solid; mp 163–165 °C; IR (KBr) ν 3442, 2920, 1663, 1604, 1510, 1466, 1307, 1249, 1178, 1033, 831, 764,728 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.90 (d, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.60 (m, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.17 – 7.14(m, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 5.46 (d, J = 1.9 Hz, 2H), 4.11 (t, J = 6.5 Hz, 2H), 2.27 (s, 6H), 1.93 (p, J = 6.5 Hz, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.53, 160.95, 160.37, 136.98, 136.54, 133.00, 128.98, 127.67, 126.71, 122.40, 122.04, 118.32, 115.27, 67.97, 66.34, 55.83, 45.25, 26.82. HRMS (ESI) m/z 338.1749 [M + H]⁺ (calcd for 338.1751, C₂₁H₂₄NO₃). HPLC purity of 98.85%.

(E)-3-(4-(4-(dimethylamino)butoxy)benzylidene)chroman-4-one (18). Yield 82%, brown yellow solid; mp 184–185 °C; IR (KBr) ν 3431, 2917, 2686, 1669, 1607, 1516, 1479, 1313, 1266, 1212, 1186, 1040, 1002, 954, 830, 792, 764 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.90 (d, J = 7.9 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.47 (d, J = 8.6 Hz, 2H), 7.17 – 7.14 (m, 1H), 7.09 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 7.7 Hz, 2H), 5.46 (s, 2H), 4.11 (d, J = 5.1 Hz, 2H), 3.11 – 3.08 (m, 2H), 2.77 (s, 6H), 1.82 – 1.77 (m, 4H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.54, 160.96, 160.26, 136.95, 136.57, 132.99, 129.05, 127.69, 126.82, 122.43, 122.05, 118.33, 115.33, 67.98, 67.54, 57.07, 43.01, 26.12, 21.51. HRMS (ESI) m/z 352.1903 [M + H]⁺ (calcd for 352.1907, C₂₂H₂₆NO₃). HPLC purity of 97.27%.

(E)-3-(4-((6-(dimethylamino)hexyl)oxy)benzylidene)chroman-4-one (19). Yield 79%, bright yellow solid; mp 181–183 °C; IR (KBr) ν 3423, 2942, 2696,1661, 1604, 1510, 1466, 1307, 1249, 1178, 1033, 831, 764,728 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.90 (d, J = 7.8 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.60 (m, 1H), 7.46 (d, J = 8.7 Hz, 2H), 7.17 – 7.14(m, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.07 (d, J = 8.1 Hz, 2H), 5.46 (d, J = 1.9 Hz, 2H), 4.11 (t, J = 6.5 Hz, 2H), 2.27 (s, 6H), 1.93 (p, J = 6.5 Hz, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.54, 160.96, 160.26, 136.95, 136.57, 132.99, 129.05, 127.69, 126.82, 122.43, 122.05, 118.33, 115.33, 67.98, 67.54, 57.07, 43.01, 26.12, 21.51. HRMS (ESI) m/z 352.1903 [M + H]⁺ (calcd for 352.1907, C₂₂H₂₆NO₃). HPLC purity of 97.27%.
1513, 1475, 1326, 1266, 1215, 1190, 1042, 1036, 999, 950, 827, 783, 761 cm$^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.74 (s, 1H), 7.64 – 7.59 (m, 1H), 7.46 (d, $J = 8.6$ Hz, 2H), 7.17 – 7.14 (m, 1H), 7.07 (d, $J = 8.5$ Hz, 3H), 5.46 (d, $J = 1.9$ Hz, 2H), 4.07 (t, $J = 6.4$ Hz, 2H), 2.88 – 2.82 (m, 2H), 2.62 (s, 6H), 1.80 – 1.74 (m, 2H), 1.64 – 1.58 (m, 2H), 1.51 – 1.45 (m, 2H), 1.40 – 1.34 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.54, 160.95, 160.45, 137.00, 136.53, 133.00, 128.95, 127.68, 126.66, 122.40, 122.05, 118.32, 115.28, 68.09, 67.98, 57.96, 43.73, 28.88, 26.41, 25.64, 25.31. HRMS (ESI) m/z 380.2222 [M + H]$^+$ (calcd for 380.2220, C$_{24}$H$_{30}$NO$_3$). HPLC purity of 98.78%.

(E)-3-(4-(2-(diethylamino)ethoxy)benzylidene)chroman-4-one (20). Yield 74%, bright yellow solid; mp 49–51 °C; IR (KBr) $\nu$ 3442, 2964, 1662, 1605, 1513, 1476, 1304, 1261, 1181, 1019, 1042, 959, 844, 752 cm$^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.8$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J = 8.8$ Hz, 2H), 7.16 – 7.13 (m, 1H), 7.08 (d, $J = 8.9$ Hz, 3H), 5.46 (d, $J = 1.9$ Hz, 2H), 4.11 (t, $J = 6.1$ Hz, 2H), 2.81 (t, $J = 6.1$ Hz, 2H), 2.59 (q, $J = 7.1$ Hz, 4H), 1.00 (t, $J = 7.1$ Hz, 6H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.50, 160.95, 160.33, 136.97, 136.51, 132.99, 128.94, 127.67, 126.68, 122.37, 122.04, 118.32, 115.31, 67.98, 67.05, 51.71, 47.42, 12.33. HRMS (ESI) m/z 352.1908 [M + H]$^+$ (calcd for 352.1907, C$_{22}$H$_{26}$NO$_3$). HPLC purity of 98.19%.

(E)-3-(4-(3-(diethylamino)propoxy)benzylidene)chroman-4-one (21). Yield 67%, bright yellow solid; mp 139–140 °C; IR (KBr) $\nu$ 3443, 296, 1667, 1604,1510, 1467, 1305, 1253, 1177, 1112, 1034, 958, 831, 757, 752 cm$^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.07 (d, $J = 8.7$ Hz, 3H), 5.46 (d, $J = 1.9$ Hz,
2H), 4.10 (t, J = 6.3 Hz, 2H), 2.55 (d, J = 7.0 Hz, 2H), 2.47 (t, J = 7.1 Hz, 4H), 1.87 – 1.82 (m, 2H), 0.96 (t, J = 7.1 Hz, 6H). 13C NMR (125 MHz, DMSO-d6) δ 181.51, 160.97, 160.51, 136.99, 136.51, 133.02, 128.93, 127.68, 126.64, 122.39, 122.07, 118.33, 115.27, 68.00, 66.52, 49.07, 46.91, 27.02, 12.31. HRMS (ESI) m/z 366.2072 [M + H]+ (calcd for 366.2064, C23H28NO3). HPLC purity of 97.70%.

(E)-3-(4-(4-(diethylamino)butoxy)benzylidene)chroman-4-one (22). Yield 47%, brown yellow oil; IR (KBr) ν 3426, 2926, 1666, 1604, 1511, 1466, 1308, 1259, 1214, 1179, 1156, 1041, 828, 751 cm⁻¹; 1H NMR (500 MHz, DMSO-d6) δ 7.90 (d, J = 7.9 Hz, 1H), 7.75 (s, 1H), 7.64 – 7.59 (m, 1H), 7.48 (d, J = 8.6 Hz, 2H), 7.17 – 7.15 (m, 1H), 7.09 (t, J = 8.8 Hz, 3H), 5.46 (s, 2H), 4.13 (t, J = 5.4 Hz, 2H), 3.16 – 3.13 (m, 6H), 1.84 – 1.80 (m, 4H), 1.22 (t, J = 7.2 Hz, 6H). 13C NMR (125 MHz, DMSO-d6) δ 181.51, 160.95, 160.46, 137.00, 136.52, 133.01, 128.91, 127.67, 126.62, 122.39, 122.05, 118.32, 115.27, 68.12, 67.98, 52.25, 46.70, 31.17, 26.98, 12.08. HRMS (ESI) m/z 380.2224 [M + H]+ (calcd for 380.2220, C24H30NO3). HPLC purity of 95.91%.

(E)-3-(4-((6-(diethylamino)hexyl)oxy)benzylidene)chroman-4-one (23). Yield 71%, bright yellow solid; mp 178–179 °C; IR (KBr) ν 3442, 2924, 2674,1660, 1604, 1512, 1477, 1305, 1259, 1176, 1021, 823 cm⁻¹; 1H NMR (500 MHz, DMSO-d6) δ 7.88 (d, J = 7.8 Hz, 1H), 7.72 (s, 1H), 7.61 – 7.57 (m, 1H), 7.43 (d, J = 8.7 Hz, 2H), 7.14 – 7.11 (m, J = 7.5 Hz, 1H), 7.06 (d, J = 8.4 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 5.44 (d, J = 1.9 Hz, 2H), 4.04 (t, J = 6.5 Hz, 2H), 2.46 (d, J = 7.4 Hz, 4H), 2.39 – 2.36 (m, 2H), 1.74 (q, J = 7.5, 7.1 Hz, 2H), 1.42 – 1.37 (m, 4H), 1.35 – 1.30 (m, 2H), 0.94 (t, J = 7.4 Hz, 6H). 13C NMR (125 MHz, DMSO-d6) δ 181.52, 160.97, 160.49, 137.01, 136.52, 133.00, 128.93, 127.68, 126.64, 122.39, 118.33, 115.28, 68.16, 68.00, 52.58,
46.78, 29.08, 27.15, 25.89, 12.10. HRMS (ESI) m/z 408.2530 [M + H]^+ (calcd for 408.2533, C26H34NO3). HPLC purity of 95.19%.

(E)-3-(4-(2-(benzyl(methyl)amino)ethoxy)benzylidene)chroman-4-one  (24).
Yield 69%, bright yellow oil; IR (KBr) \( \nu \) 3442, 2924, 2674, 1660, 1604, 1512, 1477, 1305, 1259, 1176, 1021, 823 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\( d_6 \)) \( \delta \) 7.90 (d, \( J = 7.8 \) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.65 (m, 1H), 7.45 (d, \( J = 8.7 \) Hz, 2H), 7.34 (d, \( J = 4.3 \) Hz, 4H), 7.29 – 7.24 (m, 1H), 7.17 – 7.14 (m, 1H), 7.08 (d, \( J = 8.7 \) Hz, 2H), 7.07 (d, \( J = 8.5 \) Hz, 2H), 5.46 (d, \( J = 1.6 \) Hz, 2H), 4.20 (t, \( J = 5.8 \) Hz, 2H), 3.60 (s, 2H), 2.79 (t, \( J = 5.8 \) Hz, 2H), 2.27 (s, 3H). \(^{13}\)C NMR (125 MHz, DMSO-\( d_6 \)) \( \delta \) 181.12, 160.53, 159.84, 138.96, 136.57, 136.12, 132.56, 128.77, 128.56, 128.18, 127.25, 126.93, 126.31, 121.98, 121.62, 117.91, 114.92, 67.55, 66.14, 61.69, 55.13, 42.41. HRMS (ESI) m/z 400.1903 [M + H]^+ (calcd for 400.1907, C26H26NO3). HPLC purity of 99.48%.

(E)-3-(4-(3-(benzyl(methyl)amino)propoxy)benzylidene)chroman-4-one  (25).
Yield 54%, canary yellow solid; mp 78–79 °C; IR (KBr) \( \nu \) 3424, 2952, 1664, 1591, 1509, 1467, 1398, 1307, 1247, 1176, 1141, 1112, 1018, 863, 761, 731 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\( d_6 \)) \( \delta \) 7.90 (d, \( J = 7.8 \) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \( J = 8.8 \) Hz, 2H), 7.30 (d, \( J = 4.3 \) Hz, 4H), 7.26 – 7.23 (m, 1H), 7.16 – 7.13 (m, 1H), 7.07 (d, \( J = 8.3 \) Hz, 1H), 7.04 (d, \( J = 8.8 \) Hz, 2H), 5.46 (d, \( J = 2.0 \) Hz, 2H), 4.11 (t, \( J = 6.3 \) Hz, 2H), 3.50 (s, 2H), 2.50 (t, \( J = 6.5 \) Hz, 2H), 2.16 (s, 3H), 1.94 (q, \( J = 6.7 \) Hz, 2H). \(^{13}\)C NMR (125 MHz, DMSO-\( d_6 \)) \( \delta \) 181.52, 160.94, 160.45, 139.54, 137.01, 136.51, 132.98, 129.08, 128.91, 128.55, 127.67, 127.63, 122.38, 122.04, 118.32, 115.25, 67.98, 66.41, 62.05, 53.59, 42.32, 27.01. HRMS (ESI) m/z 414.2065 [M + H]^+ (calcd for 414.2064, C27H28NO3). HPLC purity of 99.38%.
(E)-3-(4-(benzyl(methyl)amino)butoxy)benzylidene)chroman-4-one  (26).

Yield 72%, bright yellow oil; IR (KBr) ν 3424, 2952, 1664, 1591, 1509, 1467, 1398, 1307, 1247, 1176, 1141, 1112, 1018, 863, 761, 731 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.8\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.7\) Hz, 2H), 7.32 (d, \(J = 6.6\) Hz, 4H), 7.27 – 7.24 (m, 1H), 7.16 – 7.13 (m, 1H), 7.08 (d, \(J = 7.9\) Hz, 2H), 7.05 (d, \(J = 8.7\) Hz, 2H), 5.46 (d, \(J = 1.4\) Hz, 2H), 4.06 (t, \(J = 6.4\) Hz, 2H), 4.47 (s, 2H), 2.40 (t, \(J = 6.9\) Hz, 2H), 2.13 (s, 3H), 1.81 – 1.75 (m, 2H), 1.67 – 1.61 (m, 2H). \(^1\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.53, 160.96, 160.45, 139.68, 137.02, 136.51, 132.98, 129.15, 128.92, 128.57, 127.68, 127.25, 126.63, 122.39, 122.06, 118.32, 115.29, 68.04, 67.99, 62.03, 56.68, 42.20, 26.84, 23.66. HRMS (ESI) m/z 428.2223 [M + H]\(^+\) (calcd for 427.2147, C\(_{28}\)H\(_{29}\)NO\(_3\)). HPLC purity of 99.63%.

(E)-3-(4-(6-(benzyl(methyl)amino)hexyl)oxy)benzylidene)chroman-4-one  (27).

Yield 72%, canary yellow solid; mp 60–62 °C; IR (KBr) ν 3444, 2921, 2850, 1667, 1604, 1511, 1465, 1309, 1257, 1211, 1182, 1155, 1041, 1017, 828, 778 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.8\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.7\) Hz, 2H), 7.32 (d, \(J = 6.7\) Hz, 4H), 7.26 – 7.23 (m, 1H), 7.16 – 7.13 (m, 1H), 7.07 (d, \(J = 7.6\) Hz, 2H), 7.06 (d, \(J = 8.7\) Hz, 2H), 5.46 (d, \(J = 1.4\) Hz, 2H), 4.05 (t, \(J = 6.5\) Hz, 2H), 3.45 (s, 2H), 2.33 (t, \(J = 7.0\) Hz, 2H), 2.12 (s, 3H), 1.79 – 1.72 (m, 2H), 1.53 – 1.46 (m, 2H), 1.45 – 1.40 (m, 2H), 1.38 – 1.34 (m, 2H). \(^1\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.50, 160.94, 160.47, 137.00, 136.51, 133.00, 129.14, 128.91, 128.58, 127.67, 127.26, 126.61, 122.38, 122.05, 118.32, 115.25, 68.13, 67.98, 62.02, 57.00, 42.23, 31.18, 29.03, 26.95, 25.82. HRMS (ESI) m/z 456.2541 [M + H]\(^+\) (calcd for 456.2541, C\(_{30}\)H\(_{34}\)NO\(_3\)). HPLC purity of 98.78%.
**{(E)}-3-(4-(2-(benzyl(ethyl)amino)ethoxy)benzylidene)chroman-4-one (28).** Yield 21%, yellow oil; IR (KBr) ν 3444, 2921, 2850, 1667, 1604, 1511, 1465, 1309, 1257, 1211, 1182, 1155, 1041, 1017, 828, 778 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) δ 7.90 (d, \(J = 7.9\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.44 (d, \(J = 8.2\) Hz, 2H), 7.39 – 7.31 (m, 5H), 7.28 – 7.21 (m, 1H), 7.15 (t, \(J = 7.5\) Hz, 1H), 7.08 (d, \(J = 8.3\) Hz, 1H), 7.04 (d, \(J = 8.2\) Hz, 2H), 5.45 (d, \(J = 2.0\) Hz, 2H), 4.14 (t, \(J = 6.0\) Hz, 2H), 3.68 (s, 2H), 2.84 (t, \(J = 6.0\) Hz, 2H), 2.60 (q, \(J = 7.1\) Hz, 2H), 1.05 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) δ 181.52, 160.97, 160.28, 140.15, 134.06, 134.08, 129.07, 128.95, 128.85, 127.76, 127.19, 126.71, 122.38, 122.06, 118.32, 115.32, 67.98, 66.84, 58.28, 51.78, 47.92, 12.28. HRMS (ESI) m/z 414.2067 [M + H]\(^+\) (calcd for 414.2064, C\(_{27}\)H\(_{28}\)NO\(_3\)). HPLC purity of 97.66%.

**{(E)}-3-(4-(3-(benzyl(ethyl)amino)propoxy)benzylidene)chroman-4-one (29).** Yield 20%, bright yellow oil; IR (KBr) ν 3395, 2922, 1670, 1603, 1510, 1466, 1306, 1258, 1217, 1177, 1155, 1022, 959, 829, 757 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) δ 7.90 (d, \(J = 7.8\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.7\) Hz, 2H), 7.33 – 7.28 (m, 4H), 7.24 – 7.21 (m, 1H), 7.16 – 7.13 (m, 1H), 7.08 (d, \(J = 7.3\) Hz, 1H), 7.02 (d, \(J = 8.7\) Hz, 2H), 5.46 (d, \(J = 1.9\) Hz, 2H), 4.09 (t, \(J = 6.3\) Hz, 2H), 3.57 (s, 2H), 2.57 (t, \(J = 6.8\) Hz, 2H), 2.48 (q, \(J = 7.1\) Hz, 2H), 1.92 – 1.87 (m, 2H), 1.00 (t, \(J = 7.1\) Hz, 3H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) δ 181.50, 160.95, 160.45, 140.28, 137.01, 136.51, 132.99, 128.93, 128.90, 128.53, 127.67, 127.09, 126.60, 122.38, 122.05, 118.32, 115.23, 67.99, 66.39, 57.94, 49.38, 47.27, 26.83, 12.13. HRMS (ESI) m/z 428.2225 [M + H]\(^+\) (calcd for 428.2220, C\(_{28}\)H\(_{30}\)NO\(_3\)). HPLC purity of 98.72%.

**{(E)}-3-(4-(4-(benzyl(ethyl)amino)butoxy)benzylidene)chroman-4-one (30).** Yield 33%, bright yellow oil; IR (KBr) ν 3443, 2951, 1664, 1593, 1509, 1475, 1385, 1309,
1252, 1178, 1111, 1014, 955, 833, 757 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J = 7.9$ Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.35 – 7.30 (m, 4H), 7.25 – 7.22 (m, 1H), 7.16 – 7.13 (m, 1H), 7.08 (d, $J = 8.3$ Hz, 1H), 7.04 (d, $J = 8.7$ Hz, 2H), 5.46 (d, $J = 1.9$ Hz, 2H), 4.03 (t, $J = 6.5$ Hz, 2H), 3.55 (s, 2H), 2.48 – 2.45 (m, 4H), 1.78 – 1.72 (m, 2H), 1.63 – 1.57 (m, 2H), 1.00 (t, $J = 7.0$ Hz, 3H).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.54, 160.95, 160.46, 140.38, 137.03, 136.51, 132.97, 128.99, 128.91, 128.53, 127.68, 127.08, 126.61, 122.38, 122.05, 118.31, 115.27, 68.03, 67.98, 57.85, 52.50, 47.11, 26.88, 23.41, 12.07. HRMS (ESI) m/z 442.2373 [M + H]$^+$ (calcd for 442.2377, C$_{29}$H$_{32}$NO$_3$). HPLC purity of 98.52%.

($E$)-3-(4-(6-(benzyl(ethyl)amino)hexyloxy)benzylidene)chroman-4-one (31).

Yield 40%, canary yellow solid; mp 159–160 °C; IR (KBr) ν 3442, 2922, 1661, 1604, 1585, 1512, 1466, 1423, 1307, 1260, 1218, 1183, 1031, 955, 825, 752, 736 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.88 (d, $J = 7.9$ Hz, 1H), 7.72 (s, 1H), 7.61 – 7.58 (m, 1H), 7.44 (d, $J = 8.6$ Hz, 2H), 7.40 – 7.28 (m, 4H), 7.28 – 7.21 (m, 1H), 7.15 – 7.12 (m, 1H), 7.06 (d, $J = 8.0$ Hz, 1H), 7.04 (d, $J = 8.6$ Hz, 2H), 5.44 (d, $J = 1.8$ Hz, 2H), 4.02 (t, $J = 6.4$ Hz, 2H), 3.51 (s, 2H), 2.37 – 2.45 (m, 2H), 1.74 – 1.69 (m, 2H), 1.49 (s, 2H), 1.40 (t, $J = 7.9$ Hz, 2H), 1.32 (q, $J = 8.4$, 7.8 Hz, 2H), 1.24 – 1.22 (m, 2H), 1.04 – 1.00 (m, 3H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.51, 160.96, 160.47, 140.21, 137.00, 136.53, 133.00, 128.95, 128.73, 128.53, 127.69, 127.23, 126.65, 122.40, 122.07, 118.32, 115.25, 68.11, 68.00, 57.85, 52.50, 47.20, 29.06, 28.97, 27.04, 25.72, 12.08. HRMS (ESI) m/z 470.2693 [M + H]$^+$ (calcd for 470.2690, C$_{31}$H$_{36}$NO$_3$). HPLC purity of 96.44%.

($E$)-3-(4-(3-(4-methylpiperazin-1-yl)propoxy)benzylidene)chroman-4-one (32).

Yield 32%, brown yellow solid; mp 90–93 °C; IR (KBr) ν 3441, 2963, 1662, 1602,
1512, 1462, 1309, 1259, 1216, 1185, 1149, 1094, 1031, 994, 801, 748 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.9\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.8\) Hz, 2H), 7.16 – 7.13 (m, 1H), 7.07 (d, \(J = 8.8\) Hz, 2H), 7.06 (d, \(J = 7.1\) Hz, 1H), 5.46 (d, \(J = 1.9\) Hz, 2H), 4.10 (t, \(J = 6.4\) Hz, 2H), 2.46 – 2.39 (m, 10H), 2.20 (s, 3H), 1.93 – 1.88 (m, 2H). \(^1^3\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.51, 160.95, 160.42, 136.98, 136.52, 133.00, 128.95, 127.67, 126.67, 122.39, 122.04, 118.32, 115.28, 67.98, 66.54, 55.15, 54.74, 53.09, 46.10, 26.57. HRMS (ESI) m/z 393.2169 [M + H]\(^+\) (calcd for 393.2173, C\(_{24}\)H\(_{29}\)NO\(_3\)). HPLC purity of 99.31%.

\((E)-3-(4-(4-(4-methylpiperazin-1-yl)butoxy)benzylidene)chroman-4-one \quad (33)\).

Yield 32%, brown yellow solid; mp 107–109 °C; IR (KBr) \(\nu\) 3441, 2932, 1659, 1603, 1511, 1464, 1310, 1259, 1218, 1180, 1161, 1099, 1019, 995, 825, 756 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.9\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.8\) Hz, 2H), 7.16 – 7.13 (m, 1H), 7.07 (d, \(J = 8.8\) Hz, 3H), 5.46 (d, \(J = 1.9\) Hz, 2H), 4.08 (t, \(J = 6.5\) Hz, 2H), 2.38 – 2.33 (m, 10H), 2.19 (s, 3H), 1.79 – 1.72 (m, 2H), 1.62 – 1.56 (m, 2H). \(^1^3\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.51, 160.95, 160.43, 137.00, 136.53, 133.00, 128.93, 127.67, 122.39, 122.05, 118.32, 115.29, 68.00, 67.98, 57.54, 54.88, 52.66, 45.79, 26.89, 23.04. HRMS (ESI) m/z 407.2337 [M + H]\(^+\) (calcd for 407.2329, C\(_{25}\)H\(_{31}\)N\(_2\)O\(_3\)). HPLC purity of 96.80%.

\((E)-3-(4-(6-(4-methylpiperazin-1-yl)hexyl)oxy)benzylidene)chroman-4-one \quad (34)\).

Yield 56%, canary yellow solid; mp 92–94 °C; IR (KBr) \(\nu\) 3441, 2932, 1659, 1603, 1511, 1464, 1310, 1259, 1218, 1180, 1161, 1099, 1019, 995, 825, 756 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.8\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.8\) Hz, 2H), 7.16 – 7.13 (m, 1H), 7.08 (d, \(J = 7.3\) Hz, 1H), 7.07 (d, \(J = 8.8\) Hz, 2H), 5.46 (d, \(J = 1.9\) Hz, 2H), 4.05 (t, \(J = 6.4\) Hz, 2H), 2.35 (s, 8H), 2.27 (t, \(J = 8.8\) Hz, 2H), 2.19 (s, 3H), 1.79 – 1.72 (m, 2H).
= 7.4 Hz, 2H), 2.17 (s, 3H), 1.78 – 1.71 (m, 2H), 1.47 – 1.41 (m, 4H), 1.36 – 1.31 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.51, 160.96, 160.49, 137.00, 136.52, 133.00, 128.93, 127.68, 126.64, 122.39, 122.07, 118.33, 115.29, 68.16, 68.00, 58.21, 55.11, 53.06, 46.09, 29.03, 27.13, 26.69, 25.89. HRMS (ESI) m/z 435.2643 [M + H]$^+$ (calcd for 435.2642, C$_{27}$H$_{35}$N$_2$O$_3$). HPLC purity of 97.18%.

(E)-3-(4-(2-(4-benzylpiperazin-1-yl)ethoxy)benzyldiene)chroman-4-one (35).
Yield 35%, brown yellow oil; IR (KBr) $\nu$ 3443, 2941, 1667, 1606, 1588, 1516, 1468, 1307, 1264, 1221, 1188, 1160, 1029, 1012, 961, 838, 740 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J$ = 7.8 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J$ = 8.8 Hz, 2H), 7.35 – 7.30 (m, 4H), 7.28 – 7.25 (m, 1H), 7.16 – 7.13 (m, 1H), 7.08 (d, $J$ = 8.0 Hz, 1H), 5.46 (d, $J$ = 1.9 Hz, 2H), 4.17 (t, $J$ = 5.7 Hz, 2H), 3.47 (s, 2H), 2.75 – 2.72 (m, 2H), 2.52 – 2.28 (m, 8H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.52, 160.97, 160.27, 136.97, 136.53, 132.98, 129.31, 129.02, 128.64, 127.69, 127.40, 126.79, 122.40, 122.06, 118.33, 115.38, 68.00, 66.15, 62.52, 56.94, 53.54, 53.05. HRMS (ESI) m/z 455.2335 [M + H]$^+$ (calcd for 455.2329, C$_{29}$H$_{31}$N$_2$O$_3$). HPLC purity of 99.93%.

(E)-3-(4-(3-(4-benzylpiperazin-1-yl)propoxy)benzyldiene)chroman-4-one (36).
Yield 15%, canary yellow solid; mp 99–102 °C; IR (KBr) $\nu$ 3432, 2935, 1664, 1605, 1510, 1463, 1308, 1255, 1151, 836, 744 cm$^{-1}$; $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.90 (d, $J$ = 7.9 Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, $J$ = 8.8 Hz, 2H), 7.35 – 7.30 (m, 4H), 7.28 – 7.25 (m, 1H), 7.16 – 7.13 (m, 1H), 7.08 (d, $J$ = 7.8, 1H), 7.07 (d, $J$ = 8.8, 2H), 5.46 (d, $J$ = 1.9 Hz, 2H), 4.09 (t, $J$ = 6.4 Hz, 2H), 3.47 (s, 2H), 2.70 – 2.50 (m, 10H), 1.93 – 1.87 (m, 2H). $^{13}$C NMR (125 MHz, DMSO-$d_6$) $\delta$ 181.51, 160.95, 160.41, 138.70, 136.98, 136.52, 133.00, 129.28, 128.95, 128.61, 127.67,
127.35, 126.67, 122.04, 118.32, 115.28, 67.98, 66.53, 62.52, 54.76, 53.26, 53.08 (2C), 31.18. HRMS (ESI) m/z 469.2487 [M + H]^+ (calcd for 469.2486, C_{30}H_{33}N_{2}O_{3}). HPLC purity of 99.60%.

\((E)-3-(4-(6-(4-benzylpiperazin-1-yl)hexyl)oxy)benzylidene)chroman-4-one\) (37).
Yield 40%, canary yellow solid; mp 74–77 °C; IR (KBr) ν 3447, 2938, 1665, 1604, 1511, 1465, 1308, 1262, 1180, 1010, 826 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.90 (d, \(J = 7.8\) Hz, 1H), 7.74 (s, 1H), 7.63 – 7.59 (m, 1H), 7.45 (d, \(J = 8.7\) Hz, 2H), 7.34 – 7.28 (m, 4H), 7.27 – 7.23 (m, 1H), 7.16 – 7.13 (m, 1H), 7.07 (d, \(J = 7.9\) Hz, 1H), 7.06 (d, \(J = 8.7\) Hz, 2H), 5.46 (d, \(J = 1.9\) Hz, 2H), 4.05 (t, \(J = 6.5\) Hz, 2H), 3.45 (s, 2H), 2.50 – 2.26 (m, 8H), 2.26 (t, \(J = 7.3\) Hz, 2H), 1.77 – 1.68 (m, 2H), 1.47 – 1.41 (m, 4H), 1.36 – 1.31 (m, 2H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.50, 160.94, 160.48, 138.73, 137.00, 136.51, 132.99, 129.25, 128.90, 128.59, 127.67, 127.31, 126.61, 122.38, 122.05, 118.32, 115.26, 68.12, 67.98, 62.58, 58.29, 53.29, 53.13, 29.01, 27.12, 26.73, 25.88. HRMS (ESI) m/z 511.2954 [M + H]^+ (calcd for 511.2955, C_{33}H_{39}N_{2}O_{3}). HPLC purity of 96.34%.

\((E)-3-(2-(2-(dimethylamino)ethoxy)benzylidene)chroman-4-one\) (38).
Yield 73%, brown yellow oil; IR (KBr) ν 3439, 2922, 1673, 1606, 1474, 1309, 1253, 1160, 1045, 1110, 1032, 995, 959, 827 cm\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 7.91 (d, \(J = 7.9\) Hz, 1H), 7.88 (s, 1H), 7.64 – 7.60 (m, 1H), 7.50 – 7.46 (m, 1H), 7.23 – 7.19 (m, 2H), 7.17 (d, \(J = 8.0\) Hz, 1H), 7.08 (d, \(J = 7.8\) Hz, 2H), 5.32 (d, \(J = 1.9\) Hz, 2H), 4.18 (t, \(J = 5.7\) Hz, 2H), 2.74 (t, \(J = 5.7\) Hz, 2H), 2.27 (s, 6H). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)) \(\delta\) 181.88, 161.20, 157.59, 136.67, 133.17, 132.12, 131.05, 130.91, 127.72, 123.00, 122.43, 122.02, 120.91, 118.38, 112.83, 68.15, 66.79, 57.85, 45.83. HRMS
(ESI) m/z 324.1591 [M + H]⁺ (calcd for 324.1594, C₂₀H₂₂NO₃). HPLC purity of 97.24%.

\((E)\)-3-(2-(3-(dimethylamino)propoxy)benzylidene)chroman-4-one (39). Yield 66%, saffron yellow oil; IR (KBr) ν 3437, 2921, 1672, 1606, 1383, 1309, 1253, 1160, 1109, 1033, 960, 838, 756 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (d, \(J = 7.9\) Hz, 1H), 7.89 (s, 1H), 7.64 – 7.60 (m, 1H), 7.50 – 7.45 (m, 1H), 7.22 – 7.20 (m, 1H), 7.18 – 7.14 (m, 2H), 7.08 (d, \(J = 8.2\) Hz, 1H), 7.07 (t, \(J = 7.6\) Hz, 1H), 5.32 (d, \(J = 1.9\) Hz, 2H), 4.11 (t, \(J = 6.3\) Hz, 2H), 2.39 (t, \(J = 7.0\) Hz, 2H), 2.15 (s, 6H), 1.91 – 1.86 (m, 2H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.81, 161.18, 157.83, 136.68, 133.00, 132.15, 130.98, 130.83, 127.73, 123.01, 122.45, 122.03, 120.78, 118.40, 112.91, 68.11, 66.82, 49.06, 45.56, 27.10. HRMS (ESI) m/z 338.1759 [M + H]⁺ (calcd for 338.1751, C₂₁H₂₄NO₃). HPLC purity of 95.64%.

\((E)\)-3-(2-(2-(diethylamino)ethoxy)benzylidene)chroman-4-one (40). Yield 40%, yellow oil; IR (KBr) ν 3444, 2968, 1673, 1606, 1475, 1382, 1309, 1253, 1145, 1110, 1019, 959, 756 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (d, \(J = 7.8\) Hz, 1H), 7.89 (s, 1H), 7.63 – 7.60 (m, 1H), 7.49 – 7.45 (m, 1H), 7.21 – 7.19 (m, 1H), 7.16 (d, \(J = 7.9\) Hz, 2H), 7.07 (d, \(J = 8.3\) Hz, 1H), 7.06 (t, \(J = 7.7\) Hz, 1H), 5.32 (d, \(J = 1.9\) Hz, 2H), 4.11 (t, \(J = 5.7\) Hz, 2H), 2.81 (t, \(J = 5.8\) Hz, 2H), 2.55 (p, \(J = 7.0\) Hz, 4H), 0.95 (t, \(J = 7.0\) Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.77, 161.21, 157.69, 136.62, 133.22, 132.05, 130.97, 130.94, 127.72, 123.04, 122.41, 122.06, 120.78, 118.38, 112.72, 68.18, 67.36, 51.52, 47.63, 12.25. HRMS (ESI) m/z 352.1991 [M + H]⁺ (calcd for 352.1907, C₂₂H₂₆NO₃). HPLC purity of 98.25%.

\((E)\)-3-(2-(3-(diethylamino)propoxy)benzylidene)chroman-4-one (41). Yield 46%, saffron yellow oil; IR (KBr) ν 3437, 2919, 1605, 1469, 1309, 1251, 1108, 1016, S16
959, 756 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 7.91 (d, \(J = 7.9\) Hz, 1H), 7.89 (s, 1H), 7.64 – 7.60 (m, 1H), 7.49 – 7.46 (m, 1H), 7.21 – 7.19 (m, 1H), 7.16 (t, \(J = 7.4\) Hz, 2H), 7.07 (d, \(J = 8.3\) Hz, 1H), 7.06 (t, \(J = 7.5\) Hz, 1H), 5.31 (d, \(J = 1.8\) Hz, 2H), 4.12 (t, \(J = 6.1\) Hz, 2H), 2.11 (s, 2H), 1.87 (s, 2H), 1.27 – 1.25 (m, 4H), 0.95 – 0.93 (m, 6H). \(^{13}\)C NMR (125 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 181.83, 161.20, 157.33, 136.75, 132.87, 132.13, 131.16, 131.02, 127.71, 123.01, 122.50, 122.03, 121.16, 118.43, 112.83, 68.07, 65.61, 48.04, 47.12, 23.70, 9.27. HRMS (ESI) m/z 322.2067 [M + H]\(^+\) (calcd for 366.2064, C\(_{23}\)H\(_{28}\)NO\(_3\)). HPLC purity of 99.78%.

\((E)\)-3-(3-(2-(dimethylamino)ethoxy)benzylidene)chroman-4-one (42). Yield 23%, saffron yellow oil; IR (KBr) \(\nu\) 3397, 2921, 1673, 1606, 1466, 1308, 1262, 1232, 1144, 1035, 756 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 7.89 (d, \(J = 7.9\) Hz, 1H), 7.86 (s, 1H), 7.62 – 7.58 (m, 1H), 7.47 – 7.43 (m, 1H), 7.20 – 7.16 (m, 2H), 7.14 (d, \(J = 6.9\) Hz, 1H), 7.06 – 7.03(m, 2H), 5.30 (d, \(J = 1.9\) Hz, 2H), 4.14 (t, \(J = 5.7\) Hz, 2H), 2.66 (t, \(J = 5.7\) Hz, 2H), 2.21 (s, 6H). \(^{13}\)C NMR (125 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 181.83, 161.20, 157.66, 136.68, 133.11, 132.13, 131.05, 130.90, 127.72, 122.97, 122.44, 122.02, 120.84, 118.40, 112.84, 68.16, 67.01, 49.06, 46.02. HRMS (ESI) m/z 324.1590[M + H]\(^+\) (calcd for 324.1594, C\(_{20}\)H\(_{22}\)NO\(_3\)). HPLC purity of 98.60%.

\((E)\)-3-(3-(3-(dimethylamino)propoxy)benzylidene)chroman-4-one (43). Yield 49%, brown yellow solid; mp 119–121 °C; IR (KBr) \(\nu\) 3445, 2945, 1673, 1605, 1466, 1308, 1262, 1231, 1162, 1035, 995, 756 cm\(^{-1}\); \(^{1}\)H NMR (500 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 7.91 (d, \(J = 7.8\) Hz, 1H), 7.75 (s, 1H), 7.65 – 7.61 (m, 1H), 7.43 (t, \(J = 7.8\) Hz, 1H), 7.16 (t, \(J = 7.5\) Hz, 1H), 7.10 – 7.06 (m, 2H), 7.05 – 7.01 (m, 2H), 5.45 (d, \(J = 1.9\) Hz, 2H), 4.09 (t, \(J = 6.4\) Hz, 2H), 2.50 (d, \(J = 8.8\) Hz, 2H), 2.26 (s, 6H), 1.95 – 1.89 (p, \(J = 6.7\) Hz, 2H). \(^{13}\)C NMR (125 MHz, DMSO-\(\text{d}_6\)) \(\delta\) 181.65, 161.14, 159.17, 137.05, 136.77,
135.59, 131.43, 130.37, 127.75, 122.88, 121.93, 118.42, 116.58, 116.43, 67.87, 66.29, 55.92, 45.27, 26.93. HRMS (ESI) m/z 338.1747 [M + H]+ (calcd for 338.1751, C21H24NO3). HPLC purity of 99.49%.

**(E)-3-(3-(2-(diethylamino)ethoxy)benzylidene)chroman-4-one (44).** Yield 32%, yellow oil; IR (KBr) ν 3444, 2968, 1674, 1605, 1383, 1308, 1262, 1232, 1144, 1035, 995, 757 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (d, J = 7.8 Hz, 1H), 7.89 (s, 1H), 7.63 – 7.60 (m, 1H), 7.49 – 7.44 (m, 1H), 7.21 – 7.19 (m, 1H), 7.15 (t, J = 7.5 Hz, 2H), 7.10 – 7.03 (m, 2H), 5.32 (d, J = 1.9 Hz, 2H), 4.11 (t, J = 5.7 Hz, 2H), 2.80 (t, J = 5.7 Hz, 2H), 2.57 – 2.52 (m, 4H), 0.95 (t, J = 7.1 Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.75, 161.19, 157.73, 136.63, 133.21, 132.06, 130.97, 130.91, 127.71, 122.99, 122.42, 122.05, 120.73, 118.38, 112.71, 68.17, 67.51, 51.53, 47.55, 12.39. HRMS (ESI) m/z 352.1909 [M + H]+ (calcd for 352.1907, C22H26NO3). HPLC purity of 97.74%.

**(E)-3-(3-(3-(diethylamino)propoxy)benzylidene)chroman-4-one (45).** Yield 59%, yellow solid; mp 145–147 °C; IR (KBr) ν 3439, 2967, 1674, 1606, 1467, 1382, 1308, 1263, 1231, 1164, 1144, 1035, 995, 756 cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 7.91 (d, J = 7.9 Hz, 1H), 7.75 (s, 1H), 7.64 – 7.61 (m, 1H), 7.44 – 7.41 (m, 1H), 7.16 (t, J = 7.5 Hz, 1H), 7.08 (d, J = 8.7 Hz, 1H), 7.07 – 7.05 (m, 1H), 7.04 – 7.00 (m, 2H), 5.44 (d, J = 1.9 Hz, 2H), 4.08 (t, J = 6.3 Hz, 2H), 2.56 – 2.53 (m, 2H), 2.47 (q, J = 7.1 Hz, 4H), 1.84 (t, J = 6.7 Hz, 2H), 0.96 (t, J = 7.1 Hz, 6H). ¹³C NMR (125 MHz, DMSO-d₆) δ 181.65, 161.13, 158.77, 136.91, 136.83, 135.65, 131.55, 130.46, 127.77, 123.22, 122.54, 121.92, 118.42, 116.69, 116.44, 67.85, 65.32, 48.60, 46.99, 23.74, 9.12. HRMS (ESI) m/z 366.2066 [M + H]+ (calcd for 366.2064, C23H28NO3). HPLC purity of 99.88%. 

S18
Biological activity

In vitro inhibition studies on eeAChE, eqBuChE and hAChE, hBuChE

Acetylcholinesterase (AChE, E.C. 3.1.1.7, from the electric eel and hAChE, E.C. 3.1.1.7, from human erythrocytes), butyrylcholinesterase (BuChE, E.C. 3.1.1.8, from equine serum and hBuChE, E.C. 3.1.1.8, from human serum), 5,5’-dithiobis- (2-nitrobenzoic acid) (Ellman's reagent, DTNB), acetylthiocholine chloride (ATC), and butylthiocholine chloride (BTC) were purchased from Sigma-Aldrich. The ChE inhibition activities of the tested compounds were assessed by Ellman's method. Firstly, the tested 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 MgCl₂•6H₂O) to the final concentration. Subsequently, 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 the compounds (0.001-100 μM) at 37°C for 5 min in 96-well plates, followed by adding 30 μL acetylthiocholine iodide (15 mM) or S-butyrylthiocholine iodide (15 mM). Finally, the absorbance was measured at different time intervals (0, 1, 2 and 3 min) at a wavelength of 405 nm. The concentration of the compound producing 50% of enzyme activity inhibition (IC₅₀) was calculated by nonlinear regression analysis of the response-concentration (log) curve, using Graph-Pad Prism program package (Graph Pad Software; San Diego, CA). Calculations were performed according to the method of Ellman et al. Results are expressed as the mean ± SD of at least three different experiments performed in triplicate.

Kinetic analysis of eeAChE inhibition
To get the mechanism of action 16, different concentrations of substrate thiocholine iodide (0.05 - 0.25 mM) were incubated with eeAChE in absence and presence of three concentrations of 16 (0.5, 1.0, 2.0 μM), and the activities were measured at different time intervals (0, 1, 2, 3 min). Lineweaver–Burk reciprocal plots were constructed by Ellman's method at different concentrations of substrate ACh. Data analysis was performed with Graph Pad Prism 4.03 software (San Diego, CA, USA). Slopes of these reciprocal plots were then plotted against the concentration of 16 in a weighted analysis and $K_i$ was determined as the intercept on the negative x-axis.

**Inhibition studies of monoamine oxidase**

To assess the inhibitory of the synthesized compounds toward hMAO-A and hMAO-B, we followed the means of the Amplex Red MAO assay. HMAO-A and hMAO-B were purchased from Sigma-Aldrich. Similarly, the tested compounds were dissolved in a certain volume DMSO and diluted to various final concentrations using sodium phosphate buffer (8g, NaCl; 0.2g, KCl; 1.44g, Na$_2$HPO$_4$; 0.2g, KH$_2$PO$_4$). 80 μl hMAO-A or hMAO-B that adjusted to obtain in our experimental conditions the same reaction velocity, i.e., to oxidize (in the control group) the same concentration of substrate, and 20 μl test compounds were incubated for 15 min at 37°C in a flat-black-bottom 96-well microtest plate placed in a dark fluorimeter chamber. And then, adding 200 μM (final concentrations) Amplex Red reagent (1 U/mL horseradish peroxidase, and 1 mM p-tyramine) as quickly as possible. The production of H$_2$O$_2$ and resorufin were quantified at 37°C using a SpectraMax Paradigm (Molecular Devices, Sunnyvale, CA) multi-mode detection platform reader based on the fluorescence generated (excitation, 545 nm; emission, 590 nm). The specific fluorescence emission was calculated after deduction of the background activity.
background activity was determined from wells containing all of the components except for the MAO 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 MAO in the presence and absence of inhibitors after subtracting the respective background.

**Reversibility and kinetic studies of hMAO-B inhibition**

To study the nature of the enzymatic inhibition reacted to 16, we determined the activity of the enzyme in the presence and in the absence of the inhibitor by the method that to examined different times (0, 15, 30, 45, 60 min) of the hMAO-B with compound. The concentration of 16 was equal to two-fold the measured IC\(_{50}\) value for the inhibition of hMAO-B and the final concentration of 16 is equal to the IC\(_{50}\). All measurements were carried out in triplicate and expressed as mean ± SD.

To explore the mechanism of action of compound 16, reciprocal plots of \(1/V\) versus \(1/S\) were constructed at different concentrations of the substrate p-tyramine (0.05 - 0.25 \(\mu\)M) by using Amplex Red MAO assay. Four various concentrations of 16 (0, 0.015, 0.030, 0.060 \(\mu\)M) were selected for the kinetic analysis of hMAO-B inhibition. The plots were assessed by a weighted least-squares analysis. The inhibition constant \(K_i\) was determined as the replot intercept on the negative \(x\)-axis and acquired by replotting the slope versus different concentrations of 16. Data analysis was performed with GraphPad Prism 4.03 software (Graph Pad Software Inc.).

**In vitro blood–brain barrier permeation assay**

The blood-brain barrier (BBB) permeation of the compound was estimated by a parallel artificial membrane permeation assay (PAMPA). Commercial drugs, PBS
(pH = 7.4), DMSO and dodecane were purchased from Sigma and Aladdin, and the porcine brain lipid (PBL) from Avanti Polar Lipids. The donor microplate with Polyvinylidene Fluoride (PVDF) membrane (pore size is 0.45 μm) and the acceptor microplate were both from Millipore. The 96-well UV plate (COSTA®) was acquired from Corning Inc. The compound first was dissolved in DMSO at a concentration of 5mg/mL and diluted 50-fold in a PBS/EtOH mixture (70:30) to final concentration of 0.1 mg/mL. The filter membrane was coated with 5 μL of PBL in dodecane (20 mg/mL). Then the acceptor 96-well microplate was filled with 300 μL of PBS/EtOH mixture (70:30) and 200 μL compounds were added to the donor wells. The acceptor filter plate was carefully placed on the donor plate to make the filter membrane can touched with buffer solution. The donor plate was carefully removed after leaving this sandwich undisturbedly incubation for 16 h at 25°C. The concentrations of test compound in the acceptor, donor and reference wells were measured with a UV plate reader (SpectraMax Plus 384, Molecular Devices, Sunnyvale, CA, USA). Each sample was analyzed at five wavelengths in four wells and in least three independent runs, and the results were given as the means ± SD. \( P_e \) was calculated using the following expression:

\[
P_e = -\ln\left(1 - \frac{\text{drug}_{\text{acceptor}}}{\text{drug}_{\text{equilibrium}}}\right)/\left[\frac{At(\text{V}_d+\text{V}_a)}{\text{V}_d\text{V}_a}\right],
\]

where \( \text{V}_d \) is the volume of donor well, \( \text{V}_a \) is the volume in the acceptor well, \( A \) is the filter area, \( t \) is the permeation time, \( \text{drug}_{\text{acceptor}} \) is the absorbance obtained in the acceptor well, and \( \text{drug}_{\text{equilibrium}} \) is the theoretical equilibrium absorbance. A plot of the experimental data versus literature values gave a good liner correlation, \( P_e \) (exp.) = 0.6022\( P_e \) (Bibl.) +0.8073 (R\(^2\) = 0.9749) (Supporting Information, Figure S1).

**Molecular modeling studies**
Molecular modeling calculations and docking studies were performed using Molecular Operating Environment (MOE) software version 2014.09 (Chemical Computing Group, Montreal, Canada). The X-ray crystallographic structure of hAChE in complex with donepezil (PDB: 4EY7), and hMAO-B in complex with flavin adenine dinucleotide (FAD) (PDB: 2V60) were obtained from the Protein Data Bank. All water molecules in PDB files were removed and hydrogen atoms were subsequently added using protonate 3D application of MOE to the protein. The compound 16 was constructed using the builder interface of the MOE program and energy minimized using MMFF94x force field. Then the compound 16 was docked into the active site of the protein via the ‘Triangle Matcher’ method, the poses were produced and then scored by ASE scoring function. The best poses of molecules were retained and both visually inspected, the interactions with binding pocket residues were analyzed.

Acute toxicity studies

The totals of 20 Kunming mice were purchased from Laboratory Animal Research Center, Nanjing University (Nanjing, China), male, and 18-22g. Mice were maintained with a 12 h light/dark cycle (light from 08:00 to 20:00) at 26-28°C and 50-60% relative humidity. Distilled water and sterilized food for mice according animal house guidelines. The mice were adapted to this environment for 4 days and fasted 12 h before experiment. Compound 16 was suspended in 0.5% carboxymethyl cellulose sodium (CMC-Na) salt and confected into different concentrations suspension (677, 1333, 2000 mg/kg). The mice were divided into 4 groups before oral administration of compound, 0 mg/kg group was given 0.5% CMC-Na. Administered volume of compound was 0.4 ml each mouse. To observe continuously for the first 4 h for any
abnormal behavior and fatality changes, intermittently for the next 24 h. All animals were sacrificed after sequentially 14 days observation. And visually examined whether the liver, heart and kidneys were damaged or not.

**In vivo assay of cognitive and memory improvement**

**Materials and animals.**

Donepezil and Scopolamine were obtained from J&K Scientific. Scopolamine was dissolved in 0.9% saline. Donepezil and test compounds were dissolved in 0.5% CMC-Na, which was also used for the negative control. Kunming mice (18-22g, male) were supplied by Laboratory Animal Research Center, Nanjing University (Nanjing, China). Mice were adapted to the environment (room temperature 26-28°C, relative humidity at 50-60%) for 4 days prior to dosing and maintained under standard conditions with a 12h:12h light-dark cycle. All procedures were approved by the China Pharmaceutical University Animal Care and Use Committee (IACUC) and were in compliance with the National Institute of Health (NIH) guidelines.

**Step-through passive avoidance test.**

To assess the learning and memory of mice, the modification of step-down passive avoidance test was performed. The apparatus was composed of a light and a dark compartment with an electrifiable grid floor. The two compartments were separated by a block with a doorway which was served as a shock free zone. A lamp (60 W positioned above the apparatus) was illuminated in the lighted box. The behavioral tests of mice were carried out one day after 7 days of treatment with compounds. The mice underwent two separate trials: a training trail and a test trail 24 h later. For training trail, mice were initially placed on the light compartment and permitted
spontaneously to enter the dark zone. The electrical foot shock (36 V) was administered once the mice crossed into the dark compartment. We used a total of 60 mice in the passive avoidance test with 10 mice were used per treatment. Compound 16 (3, 9, 27 mg/kg) and donepezil (5 mg/kg) as a positive control were orally given 1 h before each training trail. After 30 min, memory impairment was induced by intraperitoneal injection of scopolamine (3 mg/kg). Twenty-four hours after the training trial, mice were placed on the light compartment and the time for the animal to cross through the doorway was measured as latency time for test trial. An upper cut-off time was set at 400 s.

All data are expressed as mean ± SEM. Differences between groups were examined for statistical significance using one-way ANOVA with Turkey test. A $p$ value less than 0.05 denoted the presence of a statistically significant difference.

References


2. Tables of results for the PAMPA.

**Table S1.** Permeability \( (P_e \times 10^6 \text{ cm s}^{-1}) \) in the PAMPA-BBB assay for 8 commercial drugs used in the experiment validation.

<table>
<thead>
<tr>
<th>Commercial drugs</th>
<th>Bibliography</th>
<th>Experiment</th>
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<tbody>
<tr>
<td>Verapamil</td>
<td>16</td>
<td>10.11 ± 1.02</td>
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<tr>
<td>Testosterone</td>
<td>17</td>
<td>10.98 ± 1.14</td>
</tr>
<tr>
<td>Lomefloxacin</td>
<td>1.1</td>
<td>1.05 ± 0.09</td>
</tr>
<tr>
<td>Clonidine</td>
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<tr>
<td>Piroxicam</td>
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<td>1.51 ± 0.17</td>
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<tr>
<td>Corticosterone</td>
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<td>Hydrocortisone</td>
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<td>1.05 ± 0.09</td>
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<tr>
<td>β-Estradiol</td>
<td>12</td>
<td>8.00 ± 0.85</td>
</tr>
</tbody>
</table>

\(^a\) Taken from Ref. \(^b\)

\(^b\) Data are the mean ± SD of three independent experiments.
Figure S1. Lineal correlation between experimental and reported permeability of commercial drugs using the PAMPA-BBB assay. $P_e \text{(exp.)} = 0.6022 P_e \text{(bibl.)} + 0.8073 \ (R^2 = 0.9749)$. 
3. The \(^1\)H NMR, \(^{13}\)C NMR HRMS and HPLC spectra of selected compounds

Figure S2-1. \(^1\)H NMR Spectrum of 16 in DMSO
Figure S2-2. $^{13}$C NMR Spectrum of 16 in DMSO

Figure S2-3. HRMS Spectrum of 16
Figure S2-4. HPLC Spectrum of 16

Figure S3-1. $^1$H NMR Spectrum of 20 in DMSO
Figure S3-2. $^{13}$C NMR Spectrum of 20 in DMSO

Figure S3-3. HRMS Spectrum of 20
**Figure S3-4.** HPLC Spectrum of 20

**Figure S4-1.** $^1$H NMR Spectrum of 21 in DMSO
Figure S4-2. $^{13}$C NMR Spectrum of 21 in DMSO

Figure S4-3. HRMS Spectrum of 21
Figure S4-4. HPLC Spectrum of 21

Figure S5-1. $^1$H NMR Spectrum of 25 in DMSO
Figure S5-2. $^{13}$C NMR Spectrum of 25 in DMSO

Figure S5-3. HRMS Spectrum of 25
Figure S5-4. HPLC Spectrum of 25

Figure S6-1. $^1$H NMR Spectrum of 29 in DMSO
Figure S6-2. $^{13}$C NMR Spectrum of 29 in DMSO

Figure S6-3. HRMS Spectrum of 29
Figure S6-4. HPLC Spectrum of 29

Figure S7-1. $^1$H NMR Spectrum of 34 in DMSO
Figure S7-2. $^{13}$C NMR Spectrum of 34 in DMSO

Figure S7-3. HRMS Spectrum of 34
**Figure S7-4.** HPLC Spectrum of 34

**Figure S8-1.** $^1$H NMR Spectrum of 37 in DMSO
Figure S8-2. $^{13}$C NMR Spectrum of 37 in DMSO

Figure S8-3. HRMS Spectrum of 37
Figure S8-4. HPLC Spectrum of 37

Figure S9-1. $^1$H NMR Spectrum of 45 in DMSO
Figure S9-2. $^{13}$C NMR Spectrum of 45 in DMSO

Figure S9-3. HRMS Spectrum of 45
Figure S9-4. HRMS Spectrum of 45