

Diphenylbutylpiperidine-based autophagy inducers: Design, synthesis and SAR studies

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1. Materials, methods, preparation and spectroscopic data of the DPBPs

Materials and methods

For thin-layer chromatography (TLC), Silica gel plates GF254 were used and compounds were visualized by irradiation with UV light, I₂. FT-IR spectra were recorded on an AVATAR-360 spectrophotometer. ¹H and ¹³C NMR spectra were recorded on MERCURY300, Bruker DRX-400, and Bruker AV-500 spectrometers with TMS as the internal standard. HRMS were recorded by using either FTMS-7 or IonSpec 4.7 spectrometers. Elemental analyses were conducted in a Heraeus Rapid CHNO apparatus. Melting points were measured on a SGW Melting Point System apparatus and are uncorrected. All the reactions were monitored by TLC. For known compounds, a reference is cited. Yields refer to pure compounds, unless otherwise indicated.

General Procedure for preparation DPBPs

Pimozide (15a (1))

A solution of 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene)¹ (162mg, 0.5mmol), amine (1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one)² (110mg, 0.5mmol), Na₂CO₃ (159mg, 1.5mmol) and catalytic amount of KI in CH₃CN (10mL) was allowed to heat at reflux for 12h and precipitate was removed by filtration. Evaporation in vacuo, and purification by flash chromatography (DCM: MeOH = 50:1- 30:1) afforded 132mg (57%) as a white solid. Mp: 220-223 °C. ¹H NMR (300 MHz, CDCl₃) δ 10.26 (s, 1H), 6.97-7.28 (m, 12H), 4.36 (t, 1H), 3.89 (t, *J* = 8.7 Hz, 1H), 3.02 (d, *J* = 10.7 Hz, 2H), 2.38-2.46 (m, 4H), 1.99-2.12 (m, 5H), 1.78-1.82 (m, 2H), 1.47-1.49 (m, 2H); LRESIMS *m/z* 462.1[M+H]⁺ 484.1[M+ Na]⁺.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)benzo[d]oxazol-2(3H)-one (15b)

The title compound as oil was obtained in 89% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **3**³ in a similar manner as described for the preparation of **1**. IR (neat) ν 3066, 2944, 2808, 2771, 1774, 1603, 1483, 1368, 1348, 1251, 1015, 830, 755, 736, 969 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.08-7.19 (m, 8H), 6.94-6.99 (m, 4H), 4.17 (m, 1H), 3.88 (t, *J* = 6.6 Hz, 1H),

2.98-3.01 (m, 2H), 1.45-1.50 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.5, 160.1, 154.0, 142.6, 140.5, 140.4, 129.8, 129.1, 129.0, 123.5, 122.1, 115.4, 115.1, 110.1, 109.9, 58.1, 52.9, 52.6, 49.7, 33.7, 28.8, 28.4, 25.5; LRESI-MS m/z : 463.2 $[\text{M}+\text{H}]^+$, 485.4 $[\text{M}+\text{Na}]^+$; HRESI-MS m/z : 463.2194 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{28}\text{H}_{29}\text{F}_2\text{N}_2\text{O}_2$ 463.2191.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)benzo[d]thiazol-2(3H)-one (15c)

The title compound as white solid was obtained in 74% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **5**³ in a similar manner as described for the preparation of **1**; Mp: 89-91 °C. 74% IR (neat) ν 2936, 2806, 1674, 1602, 1589, 1506, 1469, 1303, 1222, 1193, 1157, 1134, 827, 744, 657 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.34-7.42 (m, 2H), 7.25 (t, $J = 7.5$ Hz, 2H), 7.10-7.19 (m, 4H), 6.97 (t, $J = 7.2$ Hz, 4H), 4.46-4.47 (m, 1H), 3.88 (t, $J = 7.5$ Hz, 1H), 2.99-3.62 (m, 2H), 2.57-2.61 (m, 2H), 2.40 (m, 2H), 2.02-2.10 (m, 4H), 1.72-1.762 (m, 2H), 1.46 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 169.7, 162.5, 160.0, 140.4, 140.3, 129.0, 128.9, 125.8, 122.6, 122.6, 122.5, 122.5, 115.3, 115.1, 58.0, 53.2, 49.6, 33.7, 27.9; LRESI-MS m/z : 479.1 $[\text{M}+\text{H}]^+$; HRESI-MS m/z : 468.2116 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{29}\text{H}_{30}\text{N}_3\text{OS}$ 468.2104.

1-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-1H-benzo[d]imidazole (15d)

The title compound as white solid was obtained in 63% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **6**⁴ in a similar manner as described for the preparation of **1**; Mp: 127-130 °C. IR (neat) ν 3051, 2945, 2809, 2770, 1602, 1509, 1489, 1457, 1286, 1222, 1157, 1130, 1013, 830, 742, 574, 541 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.98 (m, 1H), 7.80 (m, 1H), 7.42 (m, 1H), 7.26-7.28 (m, 2H), 7.17-7.26 (m, 4H), 6.97 (t, $J = 7.5$ Hz, 4H), 4.18 (m, 1H), 3.86-3.88 (m, 1H), 3.05 (s, 1H), 2.44 (m, 2H), 2.14 (m, 6H), 2.03-2.05 (m, 2H), 1.48 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.5, 160.1, 143.9, 140.4, 140.3, 133.2, 129.1, 129.0, 122.7, 122.1, 120.5, 115.4, 113.2, 109.9, 58.157, 53.7, 52.8, 49.7, 33.7, 32.1, 25.5; LRESI-MS m/z : 446.2 $[\text{M}+\text{H}]^+$; HRESI-MS m/z : 491.2249 $[\text{M}+\text{H}]^+$, calcd for

C₂₈H₂₉N₄O₂F₂ 491.2253.

1-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-5-nitro-1H-indazole (15e)

The title compound as pale yellow solid was obtained in 97% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **7**⁵ in a similar manner as described for the preparation of **1**; Mp: 113-116 °C. IR (neat) ν 2932, 2814, 2776, 1610, 1506, 1435, 1335, 1284, 1139, 1069, 907, 839, 786. cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.63 (d, J = 1.5 Hz, 1H), 8.11-8.17 (m, 2H), 7.42 (d, J = 9.6 Hz, 1H), 7.09 (dd, J = 2.7, 6.0 Hz, 4H), 6.88 (t, J = 8.7 Hz, 4H), 4.36 (m, 1H), 3.81 (t, J = 7.5 Hz, 1H), 2.96 (d, J = 11.7 Hz, 2H), 2.23-2.38 (m, 4H), 1.93-2.21 (m, 6H), 1.37-1.42 (m, 2H); ¹³C NMR (100MHz, CDCl₃) δ 162.5, 160.1, 142.2, 140.493, 140.4, 135.5, 129.1, 129.0, 123.2, 121.0, 119.0, 115.3, 115.1, 109.2, 58.0, 52.6, 49.7, 33.712, 31.3, 25.4; LRESI-MS m/z : 491.2[M+H]⁺; HRESI-MS m/z : 491.2249[M+H]⁺, calcd for C₂₈H₂₉N₄O₂F₂ 491.2253.

1-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-1H-benzo[d][1,2,3]triazole (15f)

The title compound as pale yellow solid was obtained in 56% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **13a**⁶ in a similar manner as described for the preparation of **1**; Mp: 103-106 °C. IR (neat) ν 3444, 2925, 1728, 1601, 1506, 1221, 1158, 831, 747 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.45 (t, J = 8.4 Hz, 1H), 7.36 (t, J = 8.4 Hz, 1H), 6.98-7.20 (m, 8H), 6.93-6.96 (m, 2H), 6.83-6.81 (m, 2H), 5.734 (s, 1H), 4.34 (m, 1H), 3.95-4.03 (m, 2H), 3.85-3.86 (m, 2H), 3.52-3.51 (m, 2H), 3.24-3.28 (m, 2H), 2.53 (m, 2H), 2.41-2.47 (m, 2H), 1.99-2.09 (m, 4H), 1.23-1.75 (m, 6H); ¹³C NMR (100MHz, CDCl₃) δ 162.8, 162.6, 160.4, 160.2, 145.4, 139.131, 138.9, 132.5, 129.2, 129.1, 129.1, 129.0, 128.1, 124.7, 119.8, 115.9, 115.7, 115.4, 109.9, 56.9, 49.5, 48.7, 48.3, 32.4, 31.8, 25.9, 20.2; LRESI-MS m/z : 477.2[M+H]⁺; HRESI-MS m/z : 447.2361[M+H]⁺, calcd for C₂₇H₃₉N₄F₂ 447.2354.

1-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)indoline (15g)

The title compound as white solid was obtained in 88% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **8**⁷ in a similar manner as described for the preparation of **1**; Mp: 100-102 °C. IR (neat) ν 3042, 2944, 1604, 1506, 1489, 1270, 1222, 1157, 1128, 1014, 829, 752, 569, 537 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.15-7.25 (m, 6H), 6.94-7.66 (m, 6H), 6.61 (t, J = 7.5 Hz, 1H), 6.36 (d, J = 8.1 Hz, 1H), 3.88 (t, J = 7.5 Hz, 1H), 3.49 (m, 1H), 3.375(t, J = 7.8 Hz, 2H), 3.20-3.23 (m, 2H), 2.90-2.95 (m, 2H), 2.62 (m, 2H), 2.33-2.364 (m, 1H), 2.02-2.14 (m, 4H), 1.84-1.87 (m, 2H), 1.63 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.6, 160.2, 150.4, 140.0, 130.3, 129.1, 129.0, 127.1, 124.6, 177.4, 115.5, 115.3, 106.7, 57.8, 53.0, 51.9, 49.5, 46.8, 33.5, 28.2, 26.0, 24.2; LRESI-MS m/z : 447.2[M+H]⁺, 461.2[M+Na]⁺; HRESI-MS m/z : 447.2610[M+H]⁺, calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{F}_2$ 447.2606.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-1H-indole (15h)

The title compound as white solid was obtained in 98% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **10**⁸ in a similar manner as described for the preparation of **1**; Mp:260-264 °C. IR (neat) ν 3266, 2929, 1602, 1507, 1458, 1222, 1158, 831, 743 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.11 (s, 1H), 7.53 (d, J = 6.9 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.000-7.12 (m, 6H), 6.90-6.93 (m, 4H), 2.85-2.89 (m, 1H), 2.53-2.57 (m, 2H), 2.25-2.30 (m, 2H), 1.89-1.99 (m, 6H), 1.53-1.59 (m, 2H), 1.34 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.3, 159.9, 141.3, 136.8, 129.7, 129.7, 126.4, 121.4, 119.0, 118.6, 115.7, 115.616, 115.5, 111.9, 48.8; LRESI-MS m/z : 445.1[M+H]⁺; HRESI-MS m/z : 445.2446[M+H]⁺, calcd for $\text{C}_{29}\text{H}_{31}\text{N}_2\text{F}_2$ 445.2449.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-6-fluorobenzo[d]isoxazole (15i)

The title compound as white solid was obtained in 89% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine (6-fluoro-3-(piperidin-4-yl)benzo[d]isoxazole)⁹ in a similar manner as described for the preparation of **1**; Mp: 87-89 °C. IR (neat) ν 2806, 2768, 1882, 1608, 1510, 1493,

1222, 1122, 956, 849, 826, 818, 790 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.67 (dd, J = 4.5, 8.7 Hz, 1H), 7.21-7.25 (m, 1H), 7.14-7.19 (m, 4H), 7.03-7.07 (m, 1H), 6.94-7.01 (m, 4H), 3.86 (t, J = 8.1 Hz, 1H), 2.97-3.00 (m, 3H), 2.40 (t, J = 7.5 Hz, 2H), 1.99-2.09 (m, 8H), 1.44-1.49 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 165.1, 163.8, 163.6, 162.4, 160.9, 159.998, 140.3, 129.0, 128.9, 122.5, 122.4, 117.1, 115.2, 115.0, 112.3, 112.0, 97.4, 97.1, 58.5, 53.4, 49.6, 34.4, 33.7, 30.3, 25.3; LRESI-MS m/z : 465.1 $[\text{M}+\text{H}]^+$; elemental analysis calcd(%) for $\text{C}_{28}\text{H}_{27}\text{F}_3\text{N}_2\text{O}$: C 72.40, H 5.86, N 6.03; found: C 72.37, H 5.59, N 6.02.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)isoindoline (16a)

The title compound as oil was obtained in 63% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **11**¹⁰ in a similar manner as described for the preparation of **1**. IR (neat) ν 3418 (br), 3036, 2931, 1602, 1507 (s), 1416, 1221, 1158 (br), 1072, 914, 833, 749 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.18-7.26 (m, 4H), 7.13-7.15 (m, 4H), 6.96 (t, J = 8.7 Hz, 4H), 5.29 (s, 1H), 3.89-3.94 (m, 5H), 3.14 (m, 2H), 2.90 (m, 2H), 2.44-2.45 (m, 2H), 2.04-2.07 (m, 4H), 1.82 (s, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.7, 160.2, 139.4, 129.0, 129.0, 127.2, 122.3, 115.6, 115.4, 57.1, 56.5, 49.1, 33.1, 26.8; LRESI-MS m/z : 447.2 $[\text{M}+\text{H}]^+$; HRESI-MS m/z : 447.2614 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{29}\text{H}_{33}\text{N}_2\text{F}_2$ 447.2603.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)isoindoline-1,3-dione (16b)

The title compound as oil was obtained in 35% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **12**¹¹ in a similar manner as described for the preparation of **1**. conformation isomer. LRESI-MS m/z : 475 $[\text{M}+\text{H}]^+$.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-2H-benzo[d][1,2,3]triazole (16c)

The title compound as white solid was obtained in 43% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **13b**⁶ in a similar manner as described for the preparation of **1**; Mp: 104-106 $^\circ\text{C}$. IR (neat) ν 2938, 2809, 1887,

1600, 1505, 1316, 1299, 1219, 1155, 1137, 825, 746 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.85-7.89 (m, 2H), 7.37-7.41 (m, 2H), 7.18 (m, 4H), 6.95-7.00 (m, 4H), 4.80 (s, 1H), 3.90 (t, $J = 2.5$ Hz, 1H), 3.01-3.04 (m, 2H), 2.34-2.49 (m, 6H), 2.07-2.09 (m, 2H), 1.54 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.5, 160.1, 143.9, 140.3, 129.1, 129.0, 126.2, 118.0, 115.4, 115.2, 57.902, 51.6, 49.6, 33.6, 31.2, 25.0; LRESI-MS m/z : 477.1 $[\text{M}+\text{H}]^+$; HRESI-MS m/z : 447.2350 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{27}\text{H}_{29}\text{N}_4\text{F}_2$ 447.2354.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-1H-benzo[d]imidazole (16d)

The title compound as white solid was obtained in 79% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **14a**¹² in a similar manner as described for the preparation of **1**; Mp: 110-114 °C. IR (neat) ν 2942 , 2769 , 1602 , 1507 , 1455 , 1423 , 1273 , 1222 , 1158 , 1014 , 829 , 745 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.50-7.53 (m, 2H), 7.10-7.19 (t, $J = 8.7$ Hz, 4H), 3.83 (t, $J = 8.4$ Hz, 1H), 2.99-3.03 (m, 2H), 2.44 (t, $J = 7.5$ Hz, 2H), 1.95-2.20 (m, 8H), 1.49-1.51 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 162.5, 160.1, 157.0, 140.2, 140.2, 129.0, 129.0, 122.3, 115.4, 115.2, 114.7, 58.2, 52.8, 49.5, 35.7, 33.5, 30.0, 24.6; LRESI-MS m/z : 446.1 $[\text{M}+\text{H}]^+$; HRESI-MS m/z : 446.2403 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{28}\text{H}_{30}\text{N}_3\text{F}_2$ 436.2402.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)benzo[d]oxazole (16e)

The title compound as pale yellow solid was obtained in 67% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **14b**¹² in a similar manner as described for the preparation of **1**; Mp: 192-194 °C. IR (neat) ν 3423 (br), 2930, 2664, 1603, 1569, 1507, 1456, 1222, 1158, 832, 748 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.65-7.68 (m, 1H), 7.48-7.51 (m, 1H), 7.32-7.35 (m, 2H), 7.16 (dd, $J = 5.4$, 8.4 Hz, 4H), 6.97 (t, $J = 8.4$ Hz, 4H), 3.90 (t, $J = 8.1$ Hz, 1H), 3.17 (m, 2H), 2.83-2.86 (m, 2H), 2.38-2.40 (m, 2H), 1.78-1.79 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 166.6,

162.6, 160.2, 150.5, 140.7, 139.6, 139.0, 125.1, 124.4, 119.7, 115.5, 115.3, 110.5, 57.5, 50.5, 49.5, 49.3, 33.2, 26.2, 23.0; LRESI-MS m/z : 447.1[M+H]⁺; HRESI-MS m/z : 447.2252[M+H]⁺, calcd for C₂₈H₂₉N₂OF₂ 447.2242.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)benzo[d]thiazole (16f)

The title compound as pale yellow solid was obtained in 98% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **14c**¹² in a similar manner as described for the preparation of **1**; Mp: 131-133 °C. IR (neat) ν 2941, 2812, 2774, 1601, 1505, 1443, 1277, 986, 842, 830, 767, 732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.95 (d, J = 8.4 Hz, 1H), 7.84 (t, J = 8.1 Hz, 1H), 7.44 (t, J = 7.8 Hz, 1H), 7.34 (t, J = 7.5 Hz, 1H), 7.16 (dd, J = 1.5, 6.3 Hz, 4H), 6.96 (t, J = 8.7 Hz, 4H), 3.88 (t, J = 7.5 Hz, 1H), 3.13 (t, J = 11.5 Hz, 1H), 2.97-3.01 (m, 2H), 2.42 (t, J = 7.5 Hz, 2H); ¹³C NMR (100MHz, CDCl₃) δ 162.5, 160.0, 152.9, 140.3, 140.3, 134.5, 128.9, 125.8, 124.6, 122.5, 121.5, 115.3, 115.3, 115.1, 58.4, 53.1, 49.6, 33.7, 32.0, 25.1; LRESI-MS m/z : 463.1[M+H]⁺; HRESI-MS m/z : 463.2001[M+H]⁺, calcd for C₂₈H₂₉N₂F₂S 463.2014.

1-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one (32a)

The title compound as white solid was obtained in 78% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **20**¹³ in a similar manner as described for the preparation of **1**; Mp: 110-113 °C. IR (neat): ν 3253, 2941, 1674(s), 1604, 1506, 1469, 1325, 1221, 1157, 1110, 829, 751, 735, 576 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.93-7.26 (m, 12H), 5.44 (s, 1H), 4.26 (s, 2H), 4.14-4.20 (m, 1H), 3.90 (t, J = 8.0Hz, 1H), 3.22 (d, J = 10.8Hz, 2H), 2.82-2.87 (m, 2H), 2.70 (s, 2H), 2.43 (s, 2H), 2.05 (q, J_1 = 7.6Hz, J_2 = 14.6Hz, 2H), 1.81 (d, J = 12.4Hz, 2H), 1.56-1.63(m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.6, 160.1, 156.7, 140.1, 140.1, 139.0, 138.9, 129.1, 129.1, 128.0, 125.8, 122.7, 122.4, 115.7, 115.4, 115.2, 115.2,

115.1, 114.7, 57.2, 57.0, 53.7, 53.6, 53.4, 53.2, 49.4, 42.8, 33.4, 27.3, 27.2, 27.0, 24.4;
LRESI-MS (m/z): 476.2[M+H]⁺. HRESI-MS m/z: 476.25086[M+H]⁺, calcd for
C₂₉H₃₂F₂N₃O. 476.25080.

32b

The title compound as oil was obtained in 48% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **21**¹³ in a similar manner as described for the preparation of **1**. IR(neat) v 3428, 2925, 1602, 1507, 1454, 1413, 1345, 1222, 1159, 831, 761, 714, 675 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.20-7.26 (m, 1H), 7.01-7.18 (m, 7H), 6.92-6.99 (m, 4H), 4.45 (s, 2H), 4.12 (t, *J* = 7.2Hz, 2H), 3.82-4.08 (m, 1H), 2.94-2.96 (m, 2H), 2.38 (t, *J* = 7.2Hz, 2H), 1.91-2.14 (m, 9H), 1.42-1.46 (m, 2H), 1.25 (t, *J* = 7.2Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 162.8, 162.7, 160.3, 160.3, 139.1, 139.0, 129.2, 129.1, 129.1, 129.0, 126.8, 125.1, 115.8, 115.7, 115.6, 115.5, 60.4, 48.4, 32.1, 31.9, 29.7, 20.2, 19.7, 14.2; LRESI-MS (m/z): 521.3[M+H]⁺. HRESI-MS m/z: 512.21924 [M+H]⁺, calcd for C₂₈H₃₂F₂N₃O₂S. 512.21778.

2-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-1,2,3,4-tetrahydroisoquinoline (33a)

The title compound as oil was obtained in 82% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **22**¹⁴ in a similar manner as described for the preparation of **1**. IR (neat): v 3036, 2927, 2806, 1602, 1507, 1222, 1158, 832, 736, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.07-7.27 (m, 7H), 6.91-7.02 (m, 6H), 3.89 (t, *J* = 8.0Hz, 1H), 3.68-3.77 (m, 3H), 3.20 (d, *J* = 8.0Hz, 2H), 2.85-2.94 (m, 4H), 2.61-2.75 (m, 4H), 1.96-2.19 (m, 5H), 1.63-1.80 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 162.6, 160.2, 160.2, 139.9, 139.4, 135.0, 134.0, 133.9, 133.8, 129.3, 129.2, 129.1, 128.8, 126.7, 126.5, 126.4, 125.9, 125.8, 115.7, 115.6, 115.5, 115.4, 67.7, 60.3, 57.5, 57.4, 57.3, 51.9, 51.3, 49.6, 49.3, 48.6, 45.8, 33.5, 33.3, 31.8, 29.0, 26.1, 25.6, 25.2, 23.7, 23.4, 21.0, 14.1; LRESI-MS (m/z): 461.2[M+H]⁺. HRESI-MS m/z: 461.27759[M+H]⁺, calcd for C₃₀H₃₅F₂N₂. 461.27628.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-3,4-dihydro-2H-benzo[e][1,3]oxazin-2-one (33b)

The title compound as oil was obtained in 67% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **24**¹⁵ in a similar manner as described for the preparation of **1**. IR (neat): ν 3041, 2942, 1719 (s), 1600, 1507, 1462, 1431, 1221, 1193, 913, 830, 757, 732, 646, 577 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.94-7.27 (m, 12H), 4.27-4.36 (m, 3H), 3.86 (t, J = 7.6Hz, 1H), 2.94 (d, J = 11.6Hz, 2H), 2.35 (t, J = 7.2Hz, 2H), 2.01-2.06 (m, 4H), 1.79-1.99 (m, 4H), 1.61 (s, 2H), 1.41-1.46 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.6, 160.1, 150.7, 149.5, 140.5, 140.4, 129.1, 129.0, 128.9, 125.5, 124.1, 117.6, 116.1, 115.4, 115.1, 58.2, 54.1, 52.8, 49.7, 41.7, 33.8, 28.2, 25.6. LRESI-MS (m/z): 477.3 $[\text{M}+\text{H}]^+$. HRESI-MS m/z : 477.23500 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{29}\text{H}_{31}\text{F}_2\text{N}_2\text{O}_2$. 477.23481.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)-3,4-dihydroquinazolin-2(1H)-one (33c)

The title compound as white solid was obtained in 85% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **27**¹⁵ in a similar manner as described for the preparation of **1**; Mp: 167-170 $^\circ\text{C}$. IR (neat): ν 3442, 2926, 1604, 1507, 1299, 1220, 1157, 830, 753, 707 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.95 (s, 1H), 6.80-7.21 (m, 12H), 4.27 (s, 2H), 3.87 (t, J = 8.0, 1H), 2.97-2.99 (m, 2H), 2.49-2.51 (m, 2H), 2.30-2.31 (m, 2H), 1.97-2.02 (m, 2H), 1.62- 1.64 (m, 2H), 1.50-1.51 (m, 2H), 1.22-1.25 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.7, 162.6, 160.3, 160.1, 154.6, 140.2, 139.2, 136.5, 129.3, 128.5, 127.9, 126.2, 125.6, 122.1, 117.7, 115.8, 115.7, 113.4, 57.9, 53.2, 52.7, 50.8, 49.6, 49.5, 48.6, 43.2, 33.7, 32.0, 31.9, 29.7, 27.4, 27.3, 24.8, 14.3; LRESI-MS (m/z): 476.5 $[\text{M}-\text{H}]^+$. HRESI-MS m/z : 476.25086 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{29}\text{H}_{32}\text{F}_2\text{N}_3\text{O}_2$. 476.25080.

33d

The title compound as white solid was obtained in 78% yield from

4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **28**¹⁵ in a similar manner as described for the preparation of **1**; Mp:112-114 °C. IR (neat): ν 3433, 2918, 1652, 1603, 1506, 1462, 1397, 1342, 1221, 1165, 1102, 900, 830, 799, 757, 672 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.02-7.09 (m, 6H), 6.83-6.97 (m, 6H), 6.72 (d, $J = 8.0\text{Hz}$, 1H), 4.62 (s, 2H), 3.84 (s, 1H), 3.76 (t, $J = 8.0\text{Hz}$, 1H), 3.09 (d, $J = 9.2\text{Hz}$, 2H), 2.66 (s, 2H), 2.42-2.44 (m, 2H), 2.15 (d, $J = 7.6\text{Hz}$, 2H), 1.88-1.97 (m, 2H), 1.75 (d, $J = 10.4\text{Hz}$, 2H), 1.52 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.3, 162.7, 160.3, 147.1, 146.7, 139.6, 131.6, 131.0, 129.2, 128.4, 127.8, 126.9, 124.1, 123.9, 115.4, 71.3, 70.6, 60.4, 56.6, 53.4, 52.7, 49.1, 47.5, 39.7, 37.3, 32.1, 21.0, 14.1; LRESI-MS (m/z): 512.3 $[\text{M}+\text{H}]^+$. HRESI-MS m/z : 512.21926 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{28}\text{H}_{32}\text{F}_2\text{N}_3\text{O}_2\text{S}$. 512.21778.

3-(1-(4,4-bis(4-fluorophenyl)butyl)piperidin-4-yl)benzo[d][1,2,3]triazin-4(3H)-one (33e)

The title compound as white solid was obtained in 33% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **30**¹⁵ in a similar manner as described for the preparation of **1**; Mp: 115-117 °C. IR (neat): ν 2942, 1681(s), 1603, 1506, 1463, 1333, 1221, 1059, 968, 904, 830, 778, 734, 688 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.33-8.34 (m, 1H), 8.13 (d, $J = 8.0\text{ Hz}$, 1H), 7.90-7.95 (m, 1H), 7.77 (t, $J = 7.2\text{Hz}$, 1H), 7.16-7.19 (m, 4H), 6.97 ($J = 8.8\text{Hz}$, 4H), 3.89 (t, $J = 8.0\text{Hz}$, 1H), 3.04 (d, $J = 11.6\text{Hz}$, 2H), 2.30-2.45 (m, 4H), 2.16 (t, $J = 12.0\text{Hz}$, 2H), 1.44-1.52 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 162.6, 160.1, 155.2, 143.8, 140.5, 134.7, 132.1, 129.3, 129.1, 129.0, 128.1, 125.2, 119.4, 115.3, 115.1, 60.3, 58.0, 55.0, 52.9, 49.7, 33.7, 30.7, 29.7, 25.5, 21.0, 14.1; LRESI-MS (m/z): 475.2 $[\text{M}+\text{H}]^+$. HRESI-MS m/z : 475.23105 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{28}\text{H}_{29}\text{F}_2\text{N}_4\text{O}$. 475.23039.

33f

The title compound as white solid was obtained in 39% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **31**¹⁶ in a similar manner as described for the preparation of **1**; Mp:100-103 °C. Conformation isomer. IR (neat):

ν 3390, 2922, 1600, 1505, 1435, 1404, 1221, 1021, 952, 823, 731 cm^{-1} ; LRESI-MS (m/z): 490.5[M-H]⁺. HRESI-MS m/z: 490.23064[M+H]⁺, calcd for C₂₉H₃₀F₂N₃O₂. 490.23006.

1-(1-(4,4-bis(4-(trifluoromethyl)phenyl)butyl)piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (34a)

The title compound as white solid was obtained in 98% yield from 4,4'-(4-bromobutane-1,1-diyl)bis((trifluoromethyl)benzene)¹ and amine (1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one) in a similar manner as described for the preparation of **1**; Mp: 107-110 °C. IR (neat): ν 3392, 2935, 1693, 1615, 1483, 1377, 1324, 1168, 1127, 1067, 1017, 906, 840, 827, 757, 737 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 10.6 (s, 1H), 7.47 (d, J = 7.6Hz, 2H), 7.27 (d, J = 7.6Hz, 2H), 7.21-7.22 (m, 1H), 6.93-6.94 (m, 2H), 4.29-4.31 (m, 2H), 3.97 (t, J = 7.6 Hz, 1H), 3.00-3.02 (m, 2H), 2.43-2.48 (m, 4H), 2.03-2.14 (m, 4H), 1.72 (d, J = 11.2Hz, 2H), 1.45-1.47 (m, 2H), 1.15-1.18 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 155.3, 148.2, 129.6, 129.3, 129.0, 128.4, 128.2, 125.9, 125.8, 123.0, 121.5, 121.3, 109.9, 58.4, 53.5, 51.2, 50.9; LRESI-MS (m/z): 562.5[M+H]⁺. HRESI-MS m/z: 562.22912[M+H]⁺, calcd for C₃₀H₃₀F₆N₃O. 562.22876.

1-(1-(4,4-bis(4-(trifluoromethyl)phenyl)butyl)piperidin-4-yl)indoline (34b)

The title compound as brown solid was obtained in 66% yield from 4,4'-(4-bromobutane-1,1-diyl)bis((trifluoromethyl)benzene) and amine **8** in a similar manner as described for the preparation of **1**; Mp: 89-91 °C. IR (neat) ν 3446, 2962, 1412, 1322, 1260, 1019, 864, 799, 701 cm^{-1} ; ¹H NMR (400 MHz, CDCl₃) δ 7.43-7.49 (m, 4H), 7.24-7.28 (m, 4H), 7.08-7.19 (m, 4H), 3.87-4.05 (m, 4H), 3.00 (t, J = 8.8Hz, 2H), 2.69 (s, 4H), 2.06 (t, J = 8.0Hz, 2H), 1.97 (s, 2H), 1.86-1.93 (m, 2H), 1.67 (s, 2H), 1.18 (t, J = 7.2Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 146.2, 137.9, 131.2, 128.7, 128.6, 128.2, 127.9, 127.6, 127.3, 127.1, 126.1, 124.8, 124.8, 124.7, 124.7, 124.3, 121.6, 121.3, 120.9, 118.9, 115.3, 59.3, 56.3, 55.5, 49.8, 49.5, 48.5, 48.4, 48.3, 31.6, 31.6, 28.6, 27.0, 22.1, 20.0, 13.1; LRESI-MS (m/z): 547.1[M+H]⁺. HRESI-MS

m/z: 547.25463[M+H]⁺, calcd for C₃₁H₃₃F₆N₂. 547.25424.

3-(1-(4,4-bis(4-(trifluoromethyl)phenyl)butyl)piperidin-4-yl)-1H-indole (34c)

The title compound as white solid was obtained in 66% yield from 4,4'-(4-bromobutane-1,1-diyl)bis((trifluoromethyl)benzene) and amine **10** in a similar manner as described for the preparation of **1**; Mp: 132-135 °C. IR (neat): ν 3235, 2930, 1615, 1324, 1123, 1067, 1016, 951, 829, 744, 603 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.05 (s, 1H), 7.61 (d, *J* = 7.6Hz, 1H), 7.54 (d, *J* = 8.0Hz, 4H), 7.25-7.35 (m, 5H), 7.17 (t, *J* = 7.6Hz, 1H), 7.08 (t, *J* = 7.6Hz, 1H), 6.94 (s, 1H), 4.04 (t, *J* = 7.6Hz, 1H), 3.04 (d, *J* = 11.6Hz, 2H), 2.85 (s, 1H), 2.49 (t, *J* = 7.6Hz, 4H), 2.04-2.20 (m, 6H), 1.89 (t, *J* = 11.6Hz, 2H), 1.56-1.57 (m, 2H), 1.25 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 146.9, 128.3, 128.0, 127.7, 135.3, 127.3, 127.1, 126.1, 125.5, 124.8, 124.6, 124.5, 124.4, 124.1, 121.7, 120.9, 120.1, 118.6, 118.0, 117.9, 117.9, 110.2, 57.6, 53.3, 49.9, 32.3, 32.2, 31.6, 24.2; LRESI-MS (m/z): 545.3[M+H]⁺. HRESI-MS m/z: 545.24032[M+H]⁺, calcd for C₃₁H₃₁F₆N₂. 545.23859.

2-(1-(4,4-bis(4-(trifluoromethyl)phenyl)butyl)piperidin-4-yl)isoindoline (34d)

The title compound as oil was obtained in 79% yield from 4,4'-(4-bromobutane-1,1-diyl)bis((trifluoromethyl)benzene) and amine **11** in a similar manner as described for the preparation of **1**. IR (neat): ν 3046, 2960, 1716, 1606, 1488, 1323, 1261, 868, 799, 744 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.49 (m, 4H), 7.25-7.27 (m, 4H), 6.93-6.98 (m, 2H), 6.50-6.54 (m, 1H), 6.30 (d, *J* = 7.6Hz, 1H), 4.13-4.16 (m, 1H), 3.96 (t, *J* = 8.0Hz, 1H), 3.26-3.31 (m, 2H), 2.93-3.00 (m, 2H), 2.84-2.88 (m, 2H), 2.35 (s, 2H), 0.79-0.87 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 166.3, 158.0, 146.8, 129.2, 128.0, 127.7, 127.1, 126.1, 124.6, 124.6, 123.4, 116.0, 105.7, 67.1, 52.3, 51.8, 49.4, 45.8, 37.7, 32.1, 31.5, 29.3, 27.9, 27.2, 26.1, 22.7, 21.9, 13.0, 9.9; LRESI-MS (m/z) 547.2[M+H]⁺. HRESI-MS m/z: 547.25614[M+H]⁺, calcd for C₃₁H₃₃F₆N₂. 547.25645.

2-(1-(4,4-bis(4-(trifluoromethyl)phenyl)butyl)piperidin-4-yl)-1H-benzo[d]imidazole (34e)

The title compound as white solid was obtained in 77% yield from 4,4'-(4-bromobutane-1,1-diyl)bis((trifluoromethyl)benzene) and amine **14a** in a similar manner as described for the preparation of **1**; Mp: 122-126 °C. IR (neat): ν 2943, 1617, 1455, 1324, 1121, 825, 801, 747, 599 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 6.81-7.47 (m, 12H), 3.94-3.95 (m, 1H), 2.92-2.95 (m, 2H), 2.40-2.42 (m, 2H), 1.97-2.11 (m, 4H), 1.53-1.56 (m, 4H), 1.18-1.19 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 155.9, 146.7, 128.4, 128.0, 127.7, 127.4, 127.0, 126.9, 126.1, 124.6, 124.6, 124.6, 124.5, 124.4, 121.7, 121.3, 59.4, 57.1, 52.0, 49.8, 34.9, 31.9, 29.3, 29.1, 28.6, 27.9, 23.7, 20.0, 13.1, 13.0; LRESI-MS (m/z): 546.1 $[\text{M}+\text{H}]^+$. HRESI-MS m/z : 545.23812 $[\text{M}+\text{H}]^+$, calcd for $\text{C}_{31}\text{H}_{31}\text{F}_6\text{N}_2$. 545.23859.

5-(4-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidin-1-yl)-2,2-diphenylpentanenitrile (35a)

The title compound as white solid was obtained in 62% yield from 5-bromo-2,2-diphenylpentanenitrile¹ and amine (1-(piperidin-4-yl)-1H-benzo[d]imidazol-2(3H)-one) in a similar manner as described for the preparation of **1**; Mp: 220-222 °C. ^1H NMR (300 MHz, CDCl_3) δ 10.18 (s, 1H), 7.25-7.44 (m, 11H), 7.11-1.12 (m, 1H), 7.03-7.06 (m, 2H), 2.99 (d, $J = 11.4$ Hz, 2H), 2.42-2.50 (m, 6H), 1.78-1.82 (m, 2H), 1.64-1.69 (m, 2H); LRESI-MS m/z : 451.1 $[\text{M}+\text{H}]^+$, 473.1 $[\text{M}+\text{Na}]^+$.

5-(4-(indolin-1-yl)piperidin-1-yl)-2,2-diphenylpentanenitrile (35b)

The title compound as brown oil was obtained in 87% yield from 5-bromo-2,2-diphenylpentanenitrile¹ and amine **8** in a similar manner as described for the preparation of **1**. IR (neat) ν 3060, 2937, 2827, 2760, 1606, 1486, 1448, 1390, 1267, 1143, 763, 751, 700 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.25-7.41 (m, 10H), 7.03 (t, $J = 7.5$ Hz, 2H), 6.59 (t, $J = 7.2$ Hz, 1H), 6.37 (d, $J = 8.1$ Hz, 1H), 3.36 (t, $J = 8.4$ Hz, 3H), 2.90-2.99 (m, 4H), 2.41-2.46 (m, 4H), 2.30 (m, 2H), 1.63-1.78 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 151.0, 140.2, 130.4, 129.1, 128.1, 127.4, 127.0, 124.7, 122.5, 117.2, 107.0, 57.3, 53.5, 53.0, 51.8, 47.0, 37.5, 28.4, 27.4, 23.3; LRESI-MS

m/z : 436.1[M+H]⁺, 458.1[M+ Na]⁺; HRESI-MS m/z : 436.2745[M+H]⁺, calcd for C₃₀H₃₄N₃ 436.2747.

5-(4-(1H-indol-3-yl)piperidin-1-yl)-2,2-diphenylpentanenitrile (35c)

The title compound as white solid was obtained in 71% yield from 5-bromo-2,2-diphenylpentanenitrile¹ and amine **10** in a similar manner as described for the preparation of **1**; Mp: 70-73 °C. IR (neat) ν 3266, 2929, 1602, 1507, 1458, 1222, 1158, 831, 743 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.11 (s, 1H), 7.53 (d, J = 6.9 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 7.00 -7.125 (m, 6H), 6.90-6.93 (m, 4H), 2.85-2.89 (m, 1H), 2.53-2.57 (m, 2H), 2.25-2.30 (m, 2H), 1.89-1.99 (m, 6H), 1.53-1.596(m, 2H), 1.34 (t, J = 7.2 Hz, 2H); ¹³C NMR (100MHz, CDCl₃) δ 162.3, 159.9, 141.3, 136.8, 129.7, 129.7, 126.4, 121.4, 119.0, 118.6, 115.728, 115.6, 115.5, 111.9, 48.8; LRESI-MS m/z : 434.1[M+H]⁺; HRESI-MS m/z : 434.2592[M+H]⁺, calcd for C₃₀H₃₃N₃ 434.2590.

5-(4-(isoindolin-2-yl)piperidin-1-yl)-2,2-diphenylpentanenitrile (35d)

The title compound as brown oil was obtained in 65% yield from 5-bromo-2,2-diphenylpentanenitrile¹ and amine **11** in a similar manner as described for the preparation of **1**. IR (neat) ν 3029, 2942, 2774, 1683, 1597, 1494, 1468, 1450, 1357, 1126, 765, 749, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.25-7.41 (m, 10H), 7.17-7.21 (m, 4H), 3.95 (t, J = 7.2 Hz, 4H), 2.83-2.87 (m, 2H), 2.41-2.47 (m, 5H), 2.08-2.11 (m, 2H), 1.95 (m, 2H), 1.65-1.68 (m, 4H); ¹³C NMR (100MHz, CDCl₃) δ 195.0, 167.2, 164.7, 130.7, 130.6, 115.9, 115.7, 41.1, 38.5; LRESI-MS m/z : 436.1[M+H]⁺; HRESI-MS m/z : 436.2755[M+H]⁺, calcd for C₃₀H₃₄N₃ 436.2747.

5-(4-(1H-benzo[d]imidazol-2-yl)piperidin-1-yl)-2,2-diphenylpentanenitrile (35e)

The title compound as white solid was obtained in 88% yield from 5-bromo-2,2-diphenylpentanenitrile¹ and amine **14a** in a similar manner as described for the preparation of **1**; Mp: 96-99 °C. IR (neat) ν 3058, 2943, 2810, 2770, 1535, 1493, 1450, 1426, 1272, 767, 746, 699 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ

7.53 (dd, $J = 3, 6$ Hz, 2H), 7.23-7.39 (m, 10H), 7.18 (dd, $J = 3, 6$ Hz, 2H), 2.91-2.94 (m, 3H), 2.40-2.45 (m, 4H), 2.00-2.13 (m, 6H), 1.64-1.66 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 157.2, 139.8, 128.8, 127.7, 126.7, 126.6, 126.5, 122.3, 122.2, 114.7, 57.4, 52.9, 51.5, 37.1, 36.0, 30.2, 22.6; LRESI-MS m/z : 435.2[M+H] $^+$, 457.1[M+Na] $^+$; HRESI-MS m/z : 435.2539[M+H] $^+$, calcd for $\text{C}_{29}\text{H}_{31}\text{N}_4$ 435.2543.

3-(4-(4,4-bis(4-fluorophenyl)butyl)piperazin-1-yl)benzo[d]isothiazole (36)

The title compound as white solid was obtained in 98% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine 3-(piperazin-1-yl)benzo[d]isothiazole¹⁷ in a similar manner as described for the preparation of **1**; Mp: 81-83 °C. IR (neat): ν 2943, 2814, 1603, 1507, 1423, 1223, 1158, 828, 774, 738 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.89 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 8.4$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 8.4$ Hz, 4H), 6.97 (t, $J = 9.0$ Hz, 4H), 3.90 (t, $J = 7.8$ Hz, 1H), 3.54-3.56 (m, 4H), 2.61-2.63 (m, 4H), 2.46 (t, $J = 7.5$ Hz, 1H), 2.00-2.08 (m, 2H), 1.47-1.52 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.8, 162.5, 160.1, 152.7, 140.4, 129.1, 127.9, 127.5, 123.8, 120.5, 115.3, 115.1, 58.4, 52.9, 49.9, 49.7, 33.7, 25.1; LRESI-MS (m/z): 404.1[M+H] $^+$. HRESI-MS m/z : 464.1966[M+H] $^+$, calcd for $\text{C}_{27}\text{H}_{28}\text{N}_3\text{F}_2\text{S}$ 464.19665.

1-(4,4-bis(4-fluorophenyl)butyl)-1'H-spiro[piperidine-4,2'-quinazolin]-4'(3'H)-one (37)

The title compound as white solid was obtained in 98% yield from 4,4'-(4-bromobutane-1,1-diyl)bis(fluorobenzene) and amine **18** in a similar manner as described for the preparation of **1**; Mp: 191-192 °C IR (neat): ν 3351, 1642(s), 1611, 1506, 1219, 831, 767, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 7.76-7.78 (m, 1H), 7.19-7.23 (m, 1H), 7.05-7.09 (m, 4H), 6.89 (t, $J = 8.4$ Hz, 4H), 6.75-6.77 (m, 1H), 6.57-6.59 (m, 1H), 4.20 (s, 1H), 3.78 (s, 1H), 2.43 (s, 3H), 2.36-2.37 (m, 2H), 1.90-1.96 (m, 6H), 1.37-1.39 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.1, 161.5, 159.1, 144.3, 139.3, 133.1, 128.0, 127.9, 127.3, 118.1, 114.4, 114.2, 114.1, 114.0, 65.7,

56.9, 48.6, 48.2, 36.3, 32.6, 24.2; LRESI-MS (m/z): 462.3[M+H]⁺. HRESI-MS m/z: 462.23468[M+H]⁺, calcd for C₂₈H₃₀F₂N₃O₁. 462.23515.

2. Biological test method

H4-LC3 cells were cultured in the presence of indicated compounds for 4 hours, fixed with 4% paraformaldehyde (Sigma) and stained with 3 µg/ml DAPI (Sigma). Images data were collected with an ArrayScan HCS 4.0 Reader with a 20X objective (Cellomics) for DAPI-labeled nuclei and GFP-tagged intracellular proteins. The Spot Detector BioApplication was used to acquire and analyze the images after optimization. Images of 1,000 cells for each compound treatment were analyzed to obtain the average cell number per field, fluorescence spot number, area, and intensity per cell. The EC₅₀ was analyzed using GraphPad Prism 4. DMSO and rapamycin were used as negative or positive control, respectively. The percentages of changes of LC3-GFP were calculated by dividing with that of DMSO-treated samples. Each treatment was done in triplicate to obtain the mean ± SD. The images were also analyzed by using a conventional fluorescence microscope for visual inspection. The experiments were repeated three times with consistent results.

3. Notes and References of supplementary information

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- 2 Amine is commercially available.
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- 4 Amine **6** was prepared as same method as that of amine **5**, ¹H NMR (300 MHz, CDCl₃) δ 7.92 (s, 1H), 7.73 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 3.6 Hz, 1H), 7.20 (d, *J* = 3.0 Hz, 2H), 4.16-4.24 (m, 1H), 3.19-3.23 (m, 2H), 4.16-4.24 (m, 1H), 3.19-3.23 (m, 2H), 2.78 (t, *J* = 6.6 Hz, 2H), 2.06-2.09 (m, 2H), 1.92-1.99 (m, 2H); LRESI-MS m/z: 202.0[M+H]⁺, 224.1[M+ Na]⁺.
- 5 Amine **7** was prepared as same method as that of amine **5**, IR (neat) ν 3218, 3117, 2940, 2858, 1610, 1511, 1345, 1259, 1074, 962, 817, 780, 753 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.63 (d, *J* = 1.5 Hz, 1H), 8.13-8.18 (m, 2H), 7.46 (d, *J* = 9.6 Hz,

- 1H), 4.49 (t, $J = 8.7$ Hz, 1H), 3.24 (d, $J = 14.3$ Hz, 2H), 2.23-2.82 (m, 2H), 2.09-2.20 (m, 2H), 1.95-1.98 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 142.2, 140.2, 135.6, 123.1, 121.1, 119.0, 109.2, 57.3, 45.9, 32.9; LRESI-MS m/z : 3247 $[\text{M}+\text{H}]^+$.
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- 7 Amine **8**, IR (neat) ν 3389 (br), 2930, 2932, 1606, 1538, 1488, 1269, 1191, 1012, 746, 720 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 6.96 (d, $J = 7.2$ Hz, 2H), 6.52 (t, $J = 7.2$ Hz, 1H), 6.33 (d, $J = 7.2$ Hz, 1H), 3.35-3.46 (m, 1H), 6.33 (d, $J = 7.2$ Hz, 1H), 3.35-3.46 (m, 2H), 3.26-3.29 (m, 2H), 1.72 (m, 2H), 1.53-1.57 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 150.7, 130.1, 127.1, 124.4, 116.8, 16.8, 53.2, 46.8, 46.4, 29.0, 28.2; LRESI-MS m/z : 203.1 $[\text{M}+\text{H}]^+$.
- 8 S. Fonquerna,† M. Miralpeix, L. Page's, C. Puig, A. Cardu's, F. Antón, A. Ca'rdenas, D. Vilella, M. Aparici, E. Calaf, J. Prieto, J. Gras, J. M. Huerta, G. Warrelow, J. Beleta and H. Ryder, *J. Med. Chem.*, 2004, **47**, 6326.
- 9 Amine is commercially available.
- 10 Amine **10** was prepared as same method as that of amine **8**, IR (neat) ν 3352, 3258, 2933, 2833, 2788, 1479, 1353, 1327, 1147, 1064, 967, 886, 794, 755, 635 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.19-7.22 (m, 4H), 3.95 (m, 4H), 3.12-3.18 (m, 2H), 2.63-2.72 (m, 2H), 2.50-2.51 (m, 1H), 2.32 (s, 1H), 1.95-1.99 (m, 2H), 1.47-1.50 (m, 2H); ^{13}C NMR (100MHz, CDCl_3) δ 139.5, 126.6, 122.2, 60.9, 56.3, 44.8, 32.2; LRESI-MS m/z : 203.1 $[\text{M}+\text{H}]^+$.
- 11 Amine **12** was prepared as same method as that of amine **5**, LRESIMS m/z : 231 $[\text{M}+\text{H}]^+$.
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- 14 Amine **22** was prepared as same method as that of amine **8**, ^1H NMR (400 MHz, CDCl_3) δ 7.09-7.11 (m, 4H), 3.78 (s, 2H), 3.19 (d, $J = 12.4$ Hz, 2H), 2.82-2.88 (m,

4H), 2.57-2.67 (m, 3H), 2.32 (s, 1H), 1.92 (d, $J = 12.4\text{Hz}$, 2H), 1.52-1.56 (m, 2H);

LRESI-MS m/z : 217.1[M+H]⁺.

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- 17 Amine is commercially available.