Supporting Information for

Discovery of a Novel oxime ether Scaffold as Potent and Orally Bioavailable Free Fatty Acid Receptor 1 Agonists†

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Content: the physical characteristics, ^{1}H NMR, ^{13}C NMR, MS and elemental analysis data for all intermediates and target compounds reported in this study

General synthetic procedure for intermediate 2a-b

To a solution of 3-hydroxybenzyl alcohol (1 equiv) and benzyl bromide or (2-bromoethyl)benzene (1.02 equiv) in acetone was added K_2CO_3 (2 equiv) at room temperature. The reaction mixture was heated to 45 °C with stirring for 12 h. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20 : 5, v/v) as eluent to afford **2a-b**.

(3-(benzyloxy)phenyl)methanol (2a)

Yield: 89%; colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.48-7.25 (m, 6H), 7.15-7.08 (m, 1H), 6.97-6.90 (m, 2H), 5.32 (s, 1H), 5.14 (s, 2H), 4.61 (s, 2H).

(3-phenethoxyphenyl)methanol (2b)

Yield: 85%; colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.24-7.15 (m, 7H), 6.97-6.86 (m, 2H), 5.32 (s, 1H), 4.61 (s, 2H), 4.27 (t, J = 6.5 Hz, 2H), 3.10 (t, J = 6.5 Hz, 2H).

Synthesis of 2-(3-(hydroxymethyl)phenoxy)-1-phenylethan-1-one (5a)

To a solution of 3-hydroxybenzyl alcohol (1 g, 7.9 mmol) and 2-bromoacetophenone (1.5 g, 7.53

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mmol) in acetone was added K_2CO_3 (3.1 g, 22.6 mmol) at room temperature. The reaction mixture was heated to 45 °C with stirring for 12 h. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20 : 5, v/v) as eluent to afford the desired product **5a** (1.6 g, 89%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.03 (d, J = 3.6 Hz, 2H), 7.68-7.57 (m, 3H), 7.25-7.15 (m, 2H), 6.97-6.91 (m, 2H), 5.70 (s, 2H), 5.32 (s, 1H), 4.61 (s, 2H).

General synthetic procedure for intermediate 8a or 12a-c

A mixture of various α-bromoketone (1 equiv) and methoxyamine hydrochloride (1 equiv) in 15 mL of DMSO was stirred at room temperature for 8 h. The mixture was pour into 150 ml water, and extracted with ethyl acetate (3 × 15 mL), the organic fractions were combined, washed with saturated brine (2 × 15 ml) prior to drying over anhydrous sodium sulfate. After filtration and concentrate using a rotary evaporator, the residual colorless oil was used in the next step without further purification. To a solution of the obtained colorless oil (1.02 equiv) and 3-hydroxybenzyl alcohol or 4-hydroxybenzyl alcohol (1 equiv) in acetone was added K_2CO_3 (2 equiv) at room temperature. The reaction mixture was heated to 60 °C with stirring for 8 h. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20 : 5, v/v) as eluent to afford **8a or 12a-c**.

2-(3-(hydroxymethyl)phenoxy)-1-phenylethan-1-one O-methyl oxime (8a)

Yield: 81%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.94 (d, J = 3.8 Hz, 2H), 7.55-7.51 (m, 3H), 7.25-7.15 (m, 2H), 6.97-6.91 (m, 2H), 5.19 (s, 2H), 5.14 (s, 1H), 4.39 (s, 2H).

2-(4-(hydroxymethyl)phenoxy)-1-phenylethan-1-one O-methyl oxime (12a)

Yield: 86%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.72-7.64 (m, 2H), 7.39-7.32 (m, 3H), 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.19 (s, 2H), 5.13 (s, 1H), 4.38 (s, 2H), 3.98 (s, 3H).

2-(4-(hydroxymethyl)phenoxy)-1-(thiophen-2-yl)ethan-1-one O-methyl oxime (12b)

Yield: 86%; white solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.57 (d, J = 4.5 Hz, 1H), 7.49 (d, J = 3.8 Hz, 1H), 7.19 (d, J = 8.5 Hz, 2H), 7.12-7.08 (m, 1H), 6.84 (d, J = 8.5 Hz, 2H), 5.19 (s, 2H), 5.13 (s, 1H), 4.38 (s, 2H), 3.98 (s, 3H).

1-(4-(hydroxymethyl)phenoxy)propan-2-one O-methyl oxime (12c)

Yield: 80%; colorless oil; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 7.19 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.19 (s, 2H), 5.13 (s, 1H), 4.38 (s, 2H), 3.98 (s, 3H), 2.87 (s, 3H).

General synthetic procedure for target compounds 1-4 and 6-8

To a solution of the obtained benzyl alcohol (1 equiv) in dichloromethane (20 ml) was slowly added thionyl chloride (6 equiv) and a catalytic amount of DMF at room temperature. After stirring at 40 °C for 4 h, the reaction was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20:1, v/v) as eluent to afford the desired product. To a solution of the obtained chlorinated intermediates (1 equiv) and **14a** (1.1 equiv) in acetone was added K_2CO_3 (2 equiv) and a catalytic amount of KI at room temperature. The reaction mixture was heated to 45 °C with stirring overnight. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (5:1, v/v) as eluent to afford a white solid. To a solution of the obtained solid (1 equiv) in 2:3:1 THF/MeOH/H_2O (18 ml) was added LiOH·H_2O (1.5 equiv). After stirring at room temperature for 4 h, the volatiles were removed under reduced pressure. The residue was acidified with 1N hydrochloric acid solution, and then filtered and the filter cake was washed with 5 mL of water, dried in vacuum to afford a white powder. Recrystallization from 75% EtOH gave the desired compounds as colorless crystals.

2-(6-((3-(benzyloxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (1)

Yield 79%; colorless crystals; m.p. 105-107 °C; ^{1}HNMR (300 MHz, DMSO-d_6) δ: 12.33 (brs, 1H), 7.44-7.39 (m, 6H), 7.07-6.97 (m, 4H), 6.47-6.44 (m, 2H), 5.10 (s, 2H), 5.01 (s, 2H), 4.70 (t, J = 9.03 Hz, 1H), 4.22, 4.19 (dd, J = 6.93, 8.79 Hz, 1H), 3.71-3.62 (m, 1H), 2.75, 2.69 (dd, J = 5.43, 16.68 Hz, 1H), 2.52, 2.47 (dd, J = 9.07, 16.68 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.11, 160.65, 159.06, 158.38, 138.77, 136.97, 129.51, 128.38, 127.19, 127.68, 124.56, 121.89, 119.80, 113.89, 106.76, 96.73, 77.09, 69.11, 41.0, 37.03; ESI-MS *m/z*: 389.1 $[M-H]^-$. Anal. calcd. For $C_{24}H_{22}O_5$: C, 73.83; H, 5.68; Found: C, 73.81; H, 5.67.

2-(6-((3-phenethoxybenzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (2)

Yield 73%; colorless crystals; m.p. 94-96 °C; ^{1}HNMR (300 MHz, DMSO-d_6) δ: 12.35 (brs, 1H), 7.47-7.36 (m, 6H), 7.01-6.85 (m, 4H), 6.63-6.54 (m, 2H), 5.11 (s, 2H), 4.70 (t, J = 9.03 Hz, 1H), 4.27 (t, J = 6.5 Hz, 2H), 4.22, 4.19 (dd, J = 6.93, 8.79 Hz, 1H), 3.71-3.62 (m, 1H), 3.10 (t, J = 6.5

Hz, 2H), 2.75, 2.69 (dd, *J* = 5.43, 16.68 Hz, 1H), 2.52, 2.47 (dd, *J* = 9.07, 16.68 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.12, 160.67, 159.06, 157.38, 141.23, 138.75, 129.53, 128.35, 127.17, 127.65, 124.54, 121.87, 119.83, 113.89, 106.76, 96.76, 75.89, 69.18, 66.23, 41.0, 37.03, 35.23; ESI-MS *m/z*: 403.1 $[M-H]^-$. Anal. calcd. For $C_{25}H_{24}O_5$: C, 74.24; H, 5.98; Found: C, 74.21; H, 5.97.

2-(6-((3-(2-oxo-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (3)

Yield 68%; colorless crystals; m.p. 123-125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.35 (brs, 1H), 7.87-7.73 (m, 2H), 7.63-7.51 (m, 3H), 7.32-7.22 (m, 3H), 6.96-6.90 (m, 2H), 6.46 (d, *J* = 8.6 Hz, 2H), 5.68 (s, 2H), 5.16 (s, 2H), 4.68 (t, *J* = 8.7 Hz, 1H), 4.25-4.13 (m, 1H), 3.69-3.61 (m, 1H), 2.70, 2.65 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.47 (d, *J* = 16.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 193.2, 173.55, 162.11, 159.67, 158.73, 142.15, 132.62, 130.84, 129.15, 128.98, 127.91, 123.03, 122.26, 114.76, 105.26, 97.18, 75.55, 74.88, 71.67, 41.06, 37.73. ESI-MS *m/z*: 417.1 $[M-H]^-$. Anal. calcd. For $C_{25}H_{22}O_6$: C, 71.76; H, 5.30; Found: C, 71.72; H, 5.31.

2-(6-((3-(2-(methoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (4)

Yield 60%; colorless crystals; m.p. 112-114 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.68-7.57 (m, 2H), 7.49-7.35 (m, 3H), 7.32-7.20 (m, 1H), 7.19-6.96 (m, 4H), 6.46 (d, *J* = 8.6 Hz, 2H), 5.22 (s, 2H), 5.05 (s, 2H), 4.68 (t, *J* = 8.7 Hz, 1H), 4.25-4.13 (m, 1H), 3.99 (s, 3H), 3.69-3.61 (m, 1H), 2.70, 2.65 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.47 (d, *J* = 16.9 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.55, 165.78, 161.11, 159.67, 157.73, 142.15, 132.62, 130.84, 129.15, 128.98, 127.91, 123.03, 122.26, 114.76, 105.26, 97.18, 77.55, 73.88, 70.67, 61.91, 40.56, 37.74. ESI-MS *m/z*: 446.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13; Found: C, 69.75; H, 5.62; N, 3.12.

2-(6-((4-(2-(methoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (6)

Yield 67%; colorless crystals; m.p. 118-119 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.21 (brs, 1H), 7.64, 7.62 (dd, *J* = 6.5, 2.4 Hz, 2H), 7.46-7.36 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 7.7 Hz,

1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 7.9 Hz, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.66 (t, *J* = 8.9 Hz, 1H), 4.20-4.09 (m, 1H), 3.99 (s, 3H), 3.72-3.55 (m, 1H), 2.57 (d, *J* = 4.8 Hz, 1H), 2.28, 2.23 (dd, *J* = 15.6, 9.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.24, 161.09, 159.34, 157.85, 154.42, 133.59, 130.22, 129.92, 129.85, 128.83, 127.16, 125.04, 123.33, 114.73, 107.03, 97.07, 78.20, 69.43, 62.72, 59.73, 40.69, 37.85. ESI-MS *m/z*: 446.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{25}NO_6$: C, 69.79; H, 5.63; N, 3.13; Found: C, 69.74; H, 5.62; N, 3.14.

2-(6-((4-(2-(methoxyimino)-2-(thiophen-2-yl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl) acetic acid (7)

Yield 59%; colorless crystals; m.p. 108-110 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.42 (brs, 1H), 7.85 (d, *J* = 5.0 Hz, 1H), 7.64 (d, *J* = 3.6 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 2H), 7.23-7.16 (m, 1H), 7.10-7.02 (m, 3H), 6.44 (d, *J* = 7.7 Hz, 2H), 5.05 (s, 2H), 4.95 (s, 2H), 4.67 (t, *J* = 9.0 Hz, 1H), 4.25-4.12 (m, 1H), 4.03 (s, 3H), 3.67, 3.63 (dd, *J* = 13.9, 7.5 Hz, 1H), 2.66, 2.61 (dd, *J* = 16.4, 5.4 Hz, 1H), 2.43, 2.38 (dd, *J* = 16.4, 9.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.91, 167.45, 161.12, 159.56, 158.01, 129.21, 128.76, 127.86, 126.81, 125.02, 124.56, 123.57, 114.59, 105.19, 97.16, 77.74, 73.75, 68.69, 62.86, 40.20, 37.76. ESI-MS *m/z*: 452.1 $[M-H]^-$. Anal. calcd. For $C_{24}H_{23}NO_6S$: C, 63.56; H, 5.11; N, 3.09; Found: C, 63.51; H, 5.12; N, 3.08.

2-(6-((4-(2-(methoxyimino)propoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (8)

Yield 75%; colorless crystals; m.p. 93-94 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.31 (s, 1H), 7.35 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.54-6.37 (m, 2H), 4.95 (s, 2H), 4.68 (t, *J* = 9.1 Hz, 1H), 4.55 (s, 2H), 4.27-4.13 (m, 1H), 3.81 (s, 3H), 3.75-3.59 (m, 1H), 2.69 (dd, *J* = 16.5, 5.4 Hz, 1H), 2.50-2.34 (m, 1H), 1.86 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 175.61, 164.45, 159.56, 158.01, 157.23, 129.31, 128.76, 127.86, 126.81, 123.57, 114.59, 105.61, 97.16, 77.74, 73.75, 68.69, 61.96, 40.20, 37.76, 20.97. ESI-MS *m/z*: 384.1 $[M-H]^-$. Anal. calcd. For $C_{21}H_{23}NO_6$: C, 65.44; H, 6.02; N, 3.63; Found: C, 65.42; H, 6.01; N, 3.62.

Synthesis of target compounds 15 to 30

The target compounds **15** to **30** were obtained according to the method described for the synthesis of the compound **6**.

2-(6-((2-fluoro-4-(2-(methoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)

acetic acid (15)

Yield 71%; colorless crystals; m.p. 123-125 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.78-7.62 (m, 2H), 7.45-7.40 (m, 4H), 7.10 (d, J = 8.7 Hz, 1H), 6.92-6.72 (m, 2H), 6.44 (d, J = 6.1 Hz, 2H), 5.25 (s, 2H), 4.97 (s, 2H), 4.68 (t, J = 9.0 Hz, 1H), 4.24-4.07 (m, 1H), 3.98 (s, 3H), 3.69-3.63 (m, 1H), 2.64, 2.59 (dd, J = 16.3, 5.4 Hz, 1H), 2.44-2.27 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.11, 165.28, 161.14, 160.82, 159.36, 134.23, 131.12, 129.98, 128.87, 128.64, 127.12, 125.07, 120.12, 110.26, 107.00, 102.23, 97.08, 77.86, 74.25, 62.76, 61.95, 40.71, 37.89. ESI-MS *m/z*: 464.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}FNO_6$: C, 67.09; H, 5.20; N, 3.01; Found: C, 67.06; H, 5.21; N, 3.02.

2-(6-((3-fluoro-4-(2-(methoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl) acetic acid (16)

Yield 74%; colorless crystals; m.p. 126-128 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.39 (brs, 1H), 7.65, 7.63 (dd, J = 6.6, 2.9 Hz, 2H), 7.46-7.37 (m, 3H), 7.27-7.14 (m, 3H), 7.09 (d, J = 7.8 Hz, 1H), 6.49-6.34 (m, 2H), 5.30 (s, 2H), 4.94 (s, 2H), 4.67 (t, J = 9.0 Hz, 1H), 4.21-4.10 (m, 1H), 3.98 (s, 3H), 3.68-3.62 (m, 1H), 2.60, 2.55 (dd, J = 16.2, 5.4 Hz, 1H), 2.35, 2.30 (dd, J = 16.1, 9.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.30, 161.11, 159.23, 153.99, 152.34, 148.79, 135.43, 134.23, 131.25, 129.96, 128.81, 127.15, 125.03, 123.14, 116.11, 115.27, 107.11, 97.17, 77.98, 73.21, 68.79, 60.72, 41.19, 38.05. ESI-MS *m/z*: 464.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}FNO_6$: C, 67.09; H, 5.20; N, 3.01; Found: C, 67.05; H, 5.21; N, 3.01.

2-(6-((3-methoxy-4-(2-(methoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (17)

Yield 58%; colorless crystals; m.p. 117-119 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (brs, 1H), 7.69-7.66 (m, 2H), 7.45-7.40 (m, 3H), 7.09 (d, J = 7.9 Hz, 1H), 6.97-6.91 (m, 3H), 6.43-6.38 (m, 2H), 5.17 (s, 2H), 4.92 (s, 2H), 4.66 (t, J = 8.7 Hz, 1H), 4.32-4.07 (m, 1H), 3.96 (s, 3H), 3.77-3.72 (m, 1H), 3.67 (s, 3H), 2.69, 2.64 (dd, J = 16.6, 5.5 Hz, 1H), 2.45 (d, J = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.21, 166.49, 159.12, 158.36, 150.31, 148.91, 134.28, 131.06, 129.21, 128.76, 127.86, 127.13, 123.81, 121.24, 114.59, 112.61, 105.19, 97.16, 75.75, 73.04, 70.82, 61.23, 56.12, 41.25, 37.76. ESI-MS *m/z*: 476.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93; Found: C, 67.93; H, 5.71; N, 2.93.

2-(6-((4-(2-(methoxyimino)-2-(o-tolyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (18)

Yield 64%; colorless crystals; m.p. 105-107 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (brs, 1H), 7.47 (d, J = 7.1 Hz, 1H), 7.36-7.31 (m, 4H), 7.25 (d, J = 7.8 Hz, 2H), 6.92 (d, J = 7.8 Hz, 2H), 6.39-6.37 (m, 2H), 5.25 (s, 2H), 4.97 (s, 2H), 4.65 (t, J = 9.2 Hz, 1H), 4.27-4.12 (m, 1H), 4.03 (s, 3H), 3.75-3.54 (m, 1H), 2.68, 2.63 (dd, J = 16.5, 5.4 Hz, 1H), 2.54 (s, 3H), 2.43-2.36 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.46, 164.65, 161.67, 159.73, 157.42, 135.12, 130.95, 129.87, 125.21, 124.53, 123.78, 122.25, 118.28, 117.95, 116.34, 107.26, 97.17, 77.56, 73.23, 69.41, 62.94, 40.75, 37.82, 20.13. ESI-MS *m/z*: 460.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04; Found: C, 70.24; H, 5.91; N, 3.03.

2-(6-((4-(2-(methoxyimino)-2-(m-tolyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (19)

Yield 69%; colorless crystals; m.p. 108-109 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.45, 7.40 (dd, J = 17.1, 9.3 Hz, 2H), 7.38-7.12 (m, 4H), 7.08 (d, J = 8.0 Hz, 1H), 6.92 (t, J = 9.0 Hz, 2H), 6.45-6.40 (m, 2H), 5.19 (s, 2H), 4.92 (s, 2H), 4.66 (t, J = 8.9 Hz, 1H), 4.24-4.07 (m, 1H), 3.98 (s, 3H), 3.70-3.48 (m, 1H), 2.55, 2.50 (dd, J = 16.2, 5.6 Hz, 1H), 2.31 (d, J = 10.6 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.21, 166.49, 159.15, 158.37, 157.32, 138.28, 133.97, 131.06, 129.21, 128.76, 127.86, 125.13, 123.81, 114.59, 105.29, 97.16, 75.65, 73.04, 70.82, 61.9, 41.25, 37.76, 21.32. ESI-MS *m/z*: 460.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04; Found: C, 70.23; H, 5.91; N, 3.03.

2-(6-((4-(2-(methoxyimino)-2-(p-tolyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (20)

Yield 78%; colorless crystals; m.p. 114-116 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.39 (brs, 1H), 7.53 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.49-6.37 (m, 2H), 5.19 (s, 2H), 4.93 (s, 2H), 4.68 (t, J = 9.0 Hz, 1H), 4.18, 4.15 (dd, J = 8.9, 6.9 Hz, 1H), 3.97 (s, 3H), 3.73-3.60 (m, 1H), 2.69, 2.64 (dd, J = 16.6, 5.5 Hz, 1H), 2.45 (d, J = 9.1 Hz, 1H), 2.30 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.30, 161.11, 159.23, 158.76, 157.99, 140.79, 131.25, 129.96, 128.81, 127.15, 125.03, 123.14, 114.11, 105.11, 102.31, 75.98,

73.21, 68.79, 60.72, 41.19, 38.15, 21.3. ESI-MS *m/z*: 460.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04; Found: C, 70.23; H, 5.91; N, 3.05.

2-(6-((4-(2-(2-fluorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (21)

Yield 72%; colorless crystals; m.p. 113-115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.47 (brs, 1H), 7.47-7.40 (m, 2H), 7.36-7.31 (m, 4H), 7.26, 7.23 (dd, J = 10.3, 5.3 Hz, 1H), 6.91 (d, J = 8.5 Hz, 2H), 6.39-6.37 (m, 2H), 5.25 (s, 2H), 4.95 (s, 2H), 4.67 (t, J = 9.0 Hz, 1H), 4.28-4.10 (m, 1H), 4.03 (s, 3H), 3.75-3.54 (m, 1H), 2.68, 2.63 (dd, J = 16.5, 5.4 Hz, 1H), 2.48-2.37 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.51, 164.63, 161.61, 159.79, 157.45, 152.83, 135.62, 129.87, 125.21, 124.53, 122.21, 118.23, 117.97, 116.37, 107.25, 97.13, 77.54, 73.26, 69.43, 62.92, 40.74, 37.86. ESI-MS *m/z*: 464.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}FNO_6$: C, 67.09; H, 5.20; N, 3.01; Found: C, 67.06; H, 5.19; N, 3.01.

2-(6-((4-(2-(3-fluorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (22)

Yield 75%; colorless crystals; m.p. 107-108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.36 (brs, 1H), 7.52-7.38 (m, 3H), 7.32 (d, J = 8.5 Hz, 2H), 7.26, 7.23 (dd, J = 10.1, 5.8 Hz, 1H), 7.09 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.43 (d, J = 7.9 Hz, 2H), 5.23 (s, 2H), 4.93 (s, 2H), 4.67 (t, J = 9.0 Hz, 1H), 4.29-4.11 (m, 1H), 4.01 (s, 3H), 3.75-3.54 (m, 1H), 2.68, 2.63 (dd, J = 16.5, 5.4 Hz, 1H), 2.48-2.37 (m, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.59, 164.67, 161.11, 159.59, 157.65, 152.87, 135.32, 129.87, 125.01, 124.54, 122.25, 118.20, 117.97, 116.37, 107.25, 97.17, 77.56, 73.21, 69.41, 62.99, 40.77, 37.82. ESI-MS *m/z*: 464.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}FNO_6$: C, 67.09; H, 5.20; N, 3.01; Found: C, 67.04; H, 5.21; N, 3.02.

2-(6-((4-(2-(4-fluorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (23)

Yield 84%; colorless crystals; m.p. 126-127 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.36 (brs, 1H), 7.68 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.23 (d, J = 8.9 Hz, 2H), 7.08 (d, J = 7.8 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.46-6.36 (m, 2H), 5.22 (s, 2H), 4.92 (s, 2H), 4.67 (t, J = 9.0 Hz, 1H), 4.16, 4.13 (dd, J = 8.8, 7.0 Hz, 1H), 3.99 (s, 3H), 3.68-3.62 (m, 1H), 2.64, 2.59 (dd, J = 16.4, 5.5 Hz, 1H), 2.41, 2.36 (dd, J = 16.4, 9.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.92, 165.2, 161.10, 159.50,

157.75, 153.66, 130.24, 129.86, 129.53, 129.42, 125.01, 122.63, 115.96, 115.68, 114.74, 107.17, 97.14, 77.78, 69.42, 62.77, 59.76, 40.76, 37.81. ESI-MS *m/z*: 464.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}FNO_6$: C, 67.09; H, 5.20; N, 3.01; Found: C, 67.03; H, 5.21; N, 3.02.

2-(6-((4-(2-(3-chlorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (24)

Yield 61%; colorless crystals; m.p. 103-105 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (brs, 1H), 7.77-7.54 (m, 2H), 7.54-7.37 (m, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 6.92, 6.88 (dd, J = 12.5, 8.8 Hz, 2H), 6.55-6.33 (m, 2H), 5.23 (s, 2H), 4.95 (s, 2H), 4.68 (t, J = 9.1 Hz, 1H), 4.18, 4.15 (dd, J = 8.9, 6.9 Hz, 1H), 4.01 (s, 3H), 3.78-3.59 (m, 1H), 2.70, 2.65 (dd, J = 16.6, 5.5 Hz, 1H), 2.44 (d, J = 7.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.44, 161.09, 159.34, 157.85, 154.42, 135.59, 134.57, 130.22, 129.92, 129.85, 128.83, 127.16, 125.04, 123.33, 114.73, 105.03, 97.07, 78.20, 69.43, 62.72, 59.75, 40.66, 37.75. ESI-MS *m/z*: 480.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}ClNO_6$: C, 64.80; H, 5.02; N, 2.91; Found: C, 64.84; H, 5.01; N, 2.92.

2-(6-((4-(2-(4-chlorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (25)

Yield 67%; colorless crystals; m.p. 122-124 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.65 (d, J = 8.6 Hz, 2H), 7.46 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.90 (d, J = 8.6 Hz, 2H), 6.52-6.36 (m, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.68 (t, J = 9.1 Hz, 1H), 4.18, 4.15 (dd, J = 8.9, 6.9 Hz, 1H), 4.00 (s, 3H), 3.76-3.61 (m, 1H), 2.69, 2.64 (dd, J = 16.6, 5.5 Hz, 1H), 2.45 (d, J = 9.0 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.55, 165.78, 161.11, 159.77, 157.72, 136.15, 132.62, 129.84, 128.98, 128.90, 125.00, 122.26, 114.76, 107.26, 97.18, 77.55, 73.88, 70.67, 61.91, 40.51, 37.54. ESI-MS *m/z*: 480.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{24}ClNO_6$: C, 64.80; H, 5.02; N, 2.91; Found: C, 64.84; H, 5.01; N, 2.91.

2-(6-((4-(2-(methoxyimino)-2-(3-(trifluoromethyl)phenyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (26)

Yield 54%; colorless crystals; m.p. 106-108 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.37 (brs, 1H), 7.93 (d, J = 11.7 Hz, 2H), 7.78 (d, J = 7.6 Hz, 1H), 7.70-7.59 (m, 1H), 7.32 (d, J = 7.7 Hz, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.89 (d, J = 7.4 Hz, 2H), 6.52-6.36 (m, 2H), 5.30 (s, 2H), 4.92 (s, 2H), 4.67 (t, J = 9.1

Hz, 1H), 4.26-4.08 (m, 1H), 4.03 (s, 3H), 3.68-3.62 (m, 1H), 2.68, 2.63 (dd, *J* = 16.7, 5.4 Hz, 1H), 2.43 (d, *J* = 9.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.11, 165.28, 159.14, 158.82, 157.36, 134.23, 131.12, 129.98, 128.87, 128.64, 127.12, 125.07, 124.34, 120.12, 114.26, 107.00, 102.08, 77.86, 74.25, 70.34, 61.95, 40.71, 37.89. ESI-MS *m/z*: 514.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{24}F_3NO_6$: C, 62.91; H, 4.69; N, 2.72; Found: C, 62.94; H, 4.68; N, 2.73.

2-(6-((4-(2-(methoxyimino)-2-(4-(trifluoromethyl)phenyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (27)

Yield 58%; colorless crystals; m.p. 119-120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.40 (brs, 1H), 7.85 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 6.91 (d, *J* = 8.3 Hz, 2H), 6.44 (d, *J* = 8.1 Hz, 2H), 5.27 (s, 2H), 4.93 (s, 2H), 4.68 (t, *J* = 9.0 Hz, 1H), 4.29-4.08 (m, 1H), 4.03 (s, 3H), 3.78-3.57 (m, 1H), 2.69, 2.64 (dd, *J* = 16.6, 5.4 Hz, 1H), 2.45 (d, *J* = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 175.44, 161.09, 159.34, 158.85, 157.42, 137.59, 133.57, 130.22, 129.92, 129.85, 128.83, 127.16, 125.04, 124.12, 123.33, 114.53, 105.03, 97.07, 78.20, 73.04, 69.43, 61.72, 41.12, 37.75. ESI-MS *m/z*: 514.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{24}F_3NO_6$: C, 62.91; H, 4.69; N, 2.72; Found: C, 62.95; H, 4.68; N, 2.72.

2-(6-((4-(2-(methoxyimino)-2-(4-methoxyphenyl)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (28)

Yield 62%; colorless crystals; m.p. 117-118 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.37 (brs, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.5 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 1H), 7.00-6.87 (m, 4H), 6.49-6.36 (m, 2H), 5.18 (s, 2H), 4.92 (s, 2H), 4.66 (t, *J* = 9.0 Hz, 1H), 4.16, 4.13 (dd, *J* = 8.8, 7.0 Hz, 1H), 3.96 (s, 3H), 3.77 (s, 3H), 3.70-3.60 (m, 1H), 2.61, 2.56 (dd, *J* = 16.2, 5.4 Hz, 1H), 2.36, 2.31 (dd, *J* = 16.2, 9.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.58, 168.01, 159.01, 158.97, 157.43, 155.24, 153.39, 148.54, 130.57, 129.68, 129.36, 128.10, 124.52, 114.71, 114.25, 113.78, 113.47, 106.64, 96.65, 75.44, 73.45, 70.83, 62.04, 55.14, 40.52, 37.51. ESI-MS *m/z*: 476.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93; Found: C, 67.93; H, 5.71; N, 2.92.

2-(6-((4-(2-(2,4-difluorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (29)

Yield 53%; colorless crystals; m.p. 120-122 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (brs, 1H), 7.77-7.54 (m, 1H), 7.54-7.37 (m, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 6.92 (d, J = 8.5 Hz, 2H), 6.55-6.33 (m, 2H), 5.23 (s, 2H), 4.95 (s, 2H), 4.68 (t, J = 9.1 Hz, 1H), 4.18, 4.15 (dd, J = 8.9, 6.9 Hz, 1H), 4.03 (s, 3H), 3.78-3.59 (m, 1H), 2.71, 2.66 (dd, J = 16.6, 5.6 Hz, 1H), 2.45 (d, J = 7.6 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 175.44, 161.09, 159.34, 158.85, 157.42, 135.59, 134.57, 130.22, 129.92, 129.85, 128.83, 127.16, 125.04, 123.33, 114.53, 105.03, 97.07, 78.20, 69.43, 62.72, 59.75, 40.12, 37.75. ESI-MS *m/z*: 482.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{23}F_2NO_6$: C, 64.59; H, 4.80; N, 2.90; Found: C, 64.53; H, 4.81; N, 2.91.

2-(6-((4-(2-(3,4-dichlorophenyl)-2-(methoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (30)

Yield 57%; colorless crystals; m.p. 112-114 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (brs, 1H), 7.77-7.58 (m, 1H), 7.57-7.40 (m, 2H), 7.33 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 7.8 Hz, 1H), 6.91 (d, J = 8.6 Hz, 2H), 6.59-6.31 (m, 2H), 5.23 (s, 2H), 4.93 (s, 2H), 4.68 (t, J = 9.1 Hz, 1H), 4.29-4.06 (m, 1H), 4.01 (s, 3H), 3.76-3.54 (m, 1H), 2.70, 2.65 (dd, J = 16.6, 5.5 Hz, 1H), 2.45 (d, J = 9.1 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 173.59, 164.6, 161.11, 159.59, 157.65, 152.87, 149.6, 130.32, 129.87, 125.01, 124.54, 122.25, 118.20, 117.97, 116.37, 116.13, 114.78, 107.25, 97.17, 77.56, 73.21, 69.41, 62.99, 40.77, 37.82. ESI-MS *m/z*: 514.1 $[M-H]^-$. Anal. calcd. For $C_{26}H_{23}Cl_2NO_6$: C, 60.48; H, 4.49; N, 2.71; Found: C, 60.45; H, 4.48; N, 2.71.

Synthesis of 2-(4-(hydroxymethyl)phenoxy)-1-phenylethan-1-one (15a)

To a solution of 4-hydroxybenzyl alcohol (1 g, 7.9 mmol) and 2-bromoacetophenone (1.5 g, 7.53 mmol) in acetone was added K_2CO_3 (3.1 g, 22.6 mmol) at room temperature. The reaction mixture was heated to 45 °C with stirring for 12 h. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20 : 5, v/v) as eluent to afford the desired product **15a** (1.8 g, 97%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 8.03 (d, J = 3.6 Hz, 2H), 7.66-7.54 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.67 (s, 2H), 5.04 (t, J = 5.6 Hz, 1H), 4.38 (d, J = 5.6 Hz, 2H).

2-(4-(hydroxymethyl)phenoxy)-1-phenylethan-1-one oxime (17a)

A mixture of **15a** (3.2 g, 13.21 mmol) and hydroxylammonium chloride (1.84 g, 26.42 mmol) in 15 mL of DMSO was stirred at room temperature for 8 h. The mixture was pour into 150 ml water, and extracted with ethyl acetate (3 × 15 mL), the organic fractions were combined, washed with saturated brine (2 × 15 ml) prior to drying over anhydrous sodium sulfate. After filtration and concentrate using a rotary evaporator, the residual colorless oil was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20 : 8, v/v) as eluent to afford the desired product **17a** (3 g, 88%) as a white solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.88 (s, 1H), 7.63 (d, J = 3.6 Hz, 2H), 7.36-7.31 (m, 3H), 7.19 (d, J = 8.2 Hz, 2H), 6.87 (d, J = 8.2 Hz, 2H), 5.22 (s, 2H), 5.04 (t, J = 5.6 Hz, 1H), 4.38 (d, J = 5.6 Hz, 2H).

General synthetic procedure for target compounds 5 and 9-14

To a solution of the RBr (1.1 equiv) and **17a** (1 equiv) in acetone was added K_2CO_3 (2 equiv) at room temperature. The reaction mixture was heated to 45 °C with stirring overnight. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was used in the next step without further purification. To a solution of the obtained residue (1 equiv) in dichloromethane (20 ml) was slowly added thionyl chloride (6 equiv) and a catalytic amount of DMF at room temperature. After stirring at 40 °C for 4 h, the reaction was concentrated under reduced pressure. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (20:1, v/v) as eluent to afford the desired product. To a solution of the obtained chlorinated intermediates (1 equiv) and **14a** (1.1 equiv) in acetone was added K_2CO_3 (2 equiv) and a catalytic amount of KI at room temperature. The reaction mixture was heated to 60 °C with stirring overnight. Then the reaction mixture was cooled to room temprature followed by filtration and the filtrate was concentrated under vacuum. The residue was purified by silica gel column chromatography using a mixture of petroleum ether/ethyl acetate (5:1, v/v) as eluent to afford a white solid. To a solution of the obtained solid (1 equiv) in 2:3:1 THF/MeOH/H_2O (18 ml) was added LiOH·H_2O (1.5 equiv). After stirring at room temperature for 4 h, the volatiles were removed under reduced pressure. The residue was acidified with 1N hydrochloric acid solution, and then filtered and the filter cake was washed with 5 mL of water, dried in vacuum to afford a white powder. Recrystallization from 75% EtOH gave the desired compounds as colorless crystals.

2-(6-((4-(2-oxo-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (5)

Yield 65%; colorless crystals; m.p. 127-129 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.21 (brs, 1H), 7.64, 7.62 (dd, J = 6.5, 2.5 Hz, 2H), 7.46-7.36 (m, 3H), 7.32 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 7.9 Hz,

1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 7.9 Hz, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.66 (t, *J* = 8.9 Hz, 1H), 4.20-4.09 (m, 1H), 3.72-3.55 (m, 1H), 2.57 (d, *J* = 4.8 Hz, 1H), 2.28, 2.23 (dd, *J* = 15.6, 9.5 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 193.25, 171.24, 159.09, 158.34, 157.85, 133.59, 130.22, 129.92, 129.85, 128.83, 127.16, 125.04, 123.33, 114.73, 107.03, 97.07, 78.20, 69.43, 62.72, 42.15, 40.65, 37.87. ESI-MS *m/z*: 417.1 $[M-H]^-$. Anal. calcd. For $C_{25}H_{22}O_6$: C, 71.76; H, 5.30; Found: C, 71.74; H, 5.31.

2-(6-((4-(2-(ethoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (9)

Yield 58%; colorless crystals; m.p. 118-120 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.23 (brs, 1H), 7.65, 7.63 (dd, *J* = 6.5, 2.5 Hz, 2H), 7.45-7.35 (m, 3H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 6.41 (d, *J* = 7.9 Hz, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.66 (t, *J* = 8.9 Hz, 1H), 4.20-4.09 (m, 1H), 3.97 (q, *J* = 7.1 Hz, 2H), 3.72-3.55 (m, 1H), 2.57 (d, *J* = 4.8 Hz, 1H), 2.28, 2.23 (dd, *J* = 15.6, 9.4 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.26, 161.07, 159.35, 157.83, 154.45, 133.57, 130.25, 129.96, 129.87, 128.82, 127.16, 125.01, 123.33, 114.73, 107.03, 97.07, 78.20, 69.43, 62.72, 59.73, 42.15, 40.69, 37.85, 15.09. ESI-MS *m/z*: 460.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{27}NO_6$: C, 70.27; H, 5.90; N, 3.04; Found: C, 70.23; H, 5.91; N, 3.03.

2-(6-((4-(2-phenyl-2-(propoxyimino)ethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (10)

Yield 53%; colorless crystals; m.p. 112-114 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.86-7.56 (m, 2H), 7.51-7.37 (m, 3H), 7.31 (d, *J* = 6.7 Hz, 2H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.54-6.32 (m, 2H), 5.24 (s, 2H), 4.92 (s, 2H), 4.67 (t, *J* = 9.1 Hz, 1H), 4.38-4.27 (m, 1H), 4.16 (t, *J* = 6.4 Hz, 2H), 3.77-3.69 (m, 1H), 2.68, 2.63 (dd, *J* = 16.3, 5.0 Hz, 1H), 2.50-2.35 (m, 1H), 1.91-1.59 (m, 2H), 0.94 (t, *J* = 8.6 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.21, 166.49, 159.12, 158.36, 157.31, 134.28, 131.06, 129.21, 128.76, 127.86, 127.13, 123.81, 114.59, 112.61, 105.19, 97.16, 75.75, 73.04, 70.82, 41.25, 37.76, 20.61, 10.12. ESI-MS *m/z*: 474.2 $[M-H]^-$. Anal. calcd. For $C_{28}H_{29}NO_6$: C, 70.72; H, 6.15; N, 2.95; Found: C, 70.75; H, 6.14; N, 2.96.

2-(6-((4-(2-(isobutoxyimino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (11)

Yield 57%; colorless crystals; m.p. 106-107 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.38 (brs, 1H), 7.63, 7.61 (dd, J = 6.5, 3.0 Hz, 2H), 7.50-7.36 (m, 3H), 7.31 (d, J = 8.6 Hz, 2H), 7.09 (d, J = 7.9 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 6.52-6.33 (m, 2H), 5.25 (s, 2H), 4.94 (s, 2H), 4.67 (t, J = 9.1 Hz, 1H), 4.17, 4.14 (dd, J = 8.9, 6.9 Hz, 1H), 4.01 (d, J = 6.7 Hz, 2H), 3.75-3.57 (m, 1H), 2.69, 2.64 (dd, J = 16.6, 5.5 Hz, 1H), 2.45 (d, J = 9.1 Hz, 1H), 2.11-1.93 (m, 1H), 0.94 (d, J = 6.7 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 174.21, 166.45, 159.12, 158.36, 157.01, 134.28, 131.06, 129.21, 128.76, 127.86, 127.13, 123.81, 114.59, 105.19, 97.16, 80.74, 75.75, 73.04, 70.82, 40.25, 37.76, 26.3, 19.2. ESI-MS *m/z*: 488.2 $[M-H]^-$. Anal. calcd. For $C_{29}H_{31}NO_6$: C, 71.15; H, 6.38; N, 2.86; Found: C, 71.11; H, 6.37; N, 2.87.

2-(6-((4-(2-((cyclopropylmethoxy)imino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (12)

Yield 59%; colorless crystals; m.p. 113-115 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.34 (brs, 1H), 7.86-7.56 (m, 2H), 7.51-7.37 (m, 3H), 7.31 (d, J = 7.3 Hz, 2H), 7.09 (d, J = 7.7 Hz, 1H), 6.93 (d, J = 7.2 Hz, 2H), 6.57-6.25 (m, 2H), 5.26 (s, 2H), 4.92 (s, 2H), 4.67 (t, J = 9.0 Hz, 1H), 4.17 (t, J = 7.8 Hz, 1H), 4.05 (d, J = 7.1 Hz, 2H), 3.68-3.65 (m, 1H), 2.69, 2.64 (dd, J = 16.6, 5.3 Hz, 1H), 2.45-2.41 (m, 1H), 1.19-1.06 (m, 1H), 0.56 (d, J = 8.0 Hz, 2H), 0.34 (d, J = 4.6 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.21, 166.49, 159.12, 158.36, 157.31, 134.28, 131.06, 129.21, 128.76, 127.86, 127.13, 123.81, 114.59, 105.29, 97.16, 80.67, 75.75, 73.04, 70.82, 41.25, 37.76, 8.61, 2.32. ESI-MS *m/z*: 486.2 $[M-H]^-$. Anal. calcd. For $C_{29}H_{29}NO_6$: C, 71.44; H, 6.00; N, 2.87; Found: C, 71.41; H, 6.01; N, 2.86.

2-(6-((4-(2-((benzyloxy)imino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl) acetic acid (13)

Yield 61%; colorless crystals; m.p. 148-150 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.37 (brs, 1H), 7.65 (d, J = 11.4 Hz, 2H), 7.48-7.40 (m, 9H), 7.24 (d, J = 7.0 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 6.94-6.81 (m, 2H), 6.51-6.33 (m, 2H), 5.27 (s, 4H), 4.90 (s, 2H), 4.66 (t, J = 9.0 Hz, 1H), 4.27-4.10 (m, 1H), 3.65-3.61 (m, 1H), 2.62, 2.57 (dd, J = 16.5, 4.9 Hz, 1H), 2.38, 2.33 (dd, J = 16.4, 9.3 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 177.31, 165.38, 159.61, 158.42, 157.33, 137.53, 134.02, 131.23, 129.98, 128.87, 128.64, 127.12, 126.56, 125.07, 124.34, 123.72, 114.26, 107.00, 102.08, 77.86, 74.25, 73.82,

70.34, 40.71, 37.89. ESI-MS *m/z*: 522.2 $[M-H]^-$. Anal. calcd. For $C_{32}H_{29}NO_6$: C, 73.41; H, 5.58; N, 2.68; Found: C, 73.45; H, 5.57; N, 2.67.

2-(6-((4-(2-((2-amino-2-oxoethoxy)imino)-2-phenylethoxy)benzyl)oxy)-2,3-dihydrobenzofuran-3-yl)acetic acid (14)

Yield 45%; colorless crystals; m.p. 132-134 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.25 (brs, 1H), 9.33 (s, 1H), 8.02 (s, 1H), 7.64, 7.62 (dd, J = 6.4, 2.3 Hz, 2H), 7.46-7.37 (m, 3H), 7.35 (d, J = 8.5 Hz, 2H), 7.09 (d, J = 7.7 Hz, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.41 (d, J = 7.9 Hz, 2H), 5.22 (s, 2H), 4.93 (s, 2H), 4.87 (s, 2H), 4.65 (t, J = 8.9 Hz, 1H), 4.21-4.11 (m, 1H), 3.72-3.55 (m, 1H), 2.57 (d, J = 4.8 Hz, 1H), 2.28, 2.23 (dd, J = 15.6, 9.4 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ: 171.24, 169.37, 161.09, 159.34, 157.85, 154.42, 133.59, 130.22, 129.95, 129.86, 128.82, 127.15, 125.14, 123.35, 107.03, 97.08, 78.21, 69.43, 40.68, 37.83. ESI-MS *m/z*: 489.1 $[M-H]^-$. Anal. calcd. For $C_{27}H_{26}N_2O_7$: C, 66.11; H, 5.34; N, 5.71; Found: C, 66.14; H, 5.33; N, 5.72.