Supporting Information

Exploring glyceraldehyde derivatives inspired by empagliflozin as potential anti-heart failure agents independent of glucose-lowering effects

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Table of contents:

Chemistry section

General information

All reagents and solvents were purchased from commercial suppliers and used directly without purification. Analytical thin-layer chromatography (TLC) was performed using a silica gel plate (HSGF254, 0.2 mm thickness; Yantai Jiang you Co., China) and spots were visualized with UV light or iodine staining. ^{1}H nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker AMX-400/600 MHz NMR (TMS as internal standard). Chemical shifts were reported in parts per million (ppm, δ) relative to TMS. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). High-resolution mass spectra (HRMS) were obtained by electric ionization (El) and electrospray ionization (ESI) using a Waters GCT Premie and Waters LCT. HPLC analysis of compounds **01-20** was performed on an Agilent 1200 system equipped with a quaternary pump and a diode-array detector (DAD). The peak purity was verified by UV spectroscopy. The column used was Agilent Eclipse XDB-C18. All compounds were confirmed to be ≥ 95% pure.

Synthesis of 4-(5-bromo-2-chlorobenzyl)phenol (1a)

4-bromo-1-chloro-2-(4-ethoxybenzyl)benzene (100 g, 307.10 mmol) was dissolved in DCM (1000 mL), and the mixture was purged with N_2. BBr_3 (92.32 g, 368.52 mmol, 1.0 M in DCM) was added slowly at -78 ℃ to the mixture, then stirred at 0 ℃ for 4 h. After the starting material was consumed, monitored by TLC, ice water (500 mL) was added slowly to quench the reaction. The mixture was stirred for 10 min, and further extracted with DCM (3×500 mL). The organic phase was washed with saturated NaCl solution (500 mL), dried with anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:5) to obtain the intermediate **1a** (89.55 g, 95% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.31 (s, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 8.4, 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 3.93 (s, 2H).

Synthesis of (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl)dimethylsilane (1b)

To a solution of **1a** (89 g, 298.08 mmol) in DCM (890 mL) were added Et_3N (58.52 g, 418.72 mmol), DMAP (7.31 g, 59.82 mmol) and *tert*-butylchlorodimethylsilane (67.62 g, 448.62 mmol), and the mixture was stirred at room temperature for 4 h. After the reaction was completed, monitored by TLC, the solvent was removed *in vacuo*. The residue was dissolved with H_2O (500 mL) and extracted with EA (3×500 mL). The organic phase was washed with saturated NaCl solution (500 mL), dried with anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified using column

chromatography on silica gel (EA:PE = 1:10) to afford the intermediate **1b** (113.31 g, 92% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.50 (d, J = 2.4 Hz, 1H), 7.44 (dd, J = 8.4, 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 3.97 (s, 2H), 0.92 (s, 9H), 0.15 (s, 6H).

Synthesis of (3-(4-((tert-butyldimethylsilyl)oxy)benzyl)-4-chlorophenyl)((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (1c)

To a solution of **1b** (110 g, 267.09 mmol) in THF (1000 mL) was added *n*-BuLi (183.63 mL, 293.80 mmol, 1.6 M in THF) slowly at -78 ℃ under N_2, and the mixture was stirred at -78 ℃ for 1 h. The (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (38.24 g, 293.80 mmol) was added to the solution and the mixture was stirred at room temperature for 12 h. After the reaction was completed, monitored by TLC, the solvent was removed *in vacuo*. The residue was dissolved with H_2O (500 mL) and extracted with EA (3×500 mL). The organic phase was washed with saturated NaCl solution (500 mL), dried with anhydrous Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:10) to obtain the intermediate **1c** (61.84 g, 50% yield) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37 (d, J = 8.4 Hz, 1H), 7.31-7.20 (m, 2H), 7.07 (t, J = 8.0 Hz, 2H), 6.79-6.73 (m, 2H), 5.64-5.53 (m, 1H), 4.53-4.32 (m, 1H), 4.16-4.11 (m, 1H), 3.97 (s, 2H), 3.96-3.88 (m, 1H), 3.66-3.50 (m, 1H), 1.25 (d, J = 18.8 Hz, 3H), 1.19 (d, J = 6.0 Hz, 3H), 0.93 (s, 9H), 0.16 (s, 6H).

Synthesis of (*R*)-(3-(4-((tert-butyldimethylsilyl)oxy)benzyl)-4-chlorophenyl)(2,2-dimethyl-1,3-dioxolan-4-yl)methanone (1d)

To a solution of **1c** (61 g, 131.72 mmol) in DCM (600 mL) was added Dess-Martin Periodinane (12.09 g, 144.90 mmol) at 0 ℃, and the mixture was stirred at room temperature for 2 h. After the reaction was completed, monitored by TLC. The solution was filtered by diatomaceous earth and the filtrate was concentrated *in vacuo* to obtain the intermediate **1d** (54.65 g, 90% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.88 (d, J = 2.4 Hz, 1H), 7.83 (dd, J = 8.4, 2.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 6.78 (d, J = 8.8 Hz, 2H), 5.45 (dd, J = 7.2, 5.2 Hz, 1H), 4.25 (t, J = 8.0 Hz, 1H), 4.07-4.01 (m, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 0.92 (s, 9H), 0.15 (s, 6H).

Synthesis of (*R*)-(4-chloro-3-(4-hydroxybenzyl)phenyl)(2,2-dimethyl-1,3-dioxolan-4-yl)methanone (1e)

To a solution of **1d** (54 g, 117.12 mmol) in THF (500 mL) was added TBAF (33.64 g, 128.83 mmol) at 0 ℃ and the mixture was stirred at room temperature for 1 h. After

the reaction was completed, monitored by TLC. The solvent was removed *in vacuo*. The residue was dissolved with H_2O (250 mL) and extracted with EA (3×250 mL). The organic layer was washed with saturated NaCl solution (250 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:5) to obtain the intermediate **1e** (24.37 g, 65% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.27 (s, 1H), 7.88 (d, J = 2.4 Hz, 1H), 7.83 (dd, J = 8.4, 2.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 2H), 6.69 (d, J = 8.4 Hz, 2H), 5.47 (dd, J = 7.6, 5.2 Hz, 1H), 4.26 (t, J = 8.4 Hz, 1H), 4.06-3.99 (m, 3H), 1.36 (s, 3H), 1.29 (s, 3H).

Synthesis of (*R*)-1-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2,3-dihydroxypropan-1-one (01)

To a solution of **1e** (1.0 g, 2.17 mmol) in MeOH (10 mL) was added HCl (4 M, 1.63 mL, 6.51 mmol), and the mixture was stirred at room temperature overnight. After the reaction was completed, monitored by TLC. The solvent was removed *in vacuo*. The residue was dissolved with H_2O (50 mL) and extracted with EA (3×50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:1) to obtain the compound **01** (0.33 g, 50% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.29 (s, 1H), 7.94-7.83 (m, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 2H), 6.70 (d, J = 8.4 Hz, 2H), 5.35 (d, J = 6.5 Hz, 1H), 4.98-4.90 (m, 1H), 4.83 (t, J = 5.8 Hz, 1H), 4.01 (s, 2H), 3.74-3.58 (m, 2H). HRMS (ESI) m/z calcd for $C_{16}H_{15}ClO_4$ $[M+Cl]^-$ 341.0353, found 341.0342.

General synthesis of compounds 2a-13a

To a stirred solution of **1e** (1.0 g, 2.88 mmol) and Cs_2CO_3 (2.82 g, 8.65 mmol) in DMF (20 mL) was added iodoethane (346 μL, 4.33 mmol), and the mixture was stirred at 60 ℃ for 12 h. After the reaction was completed, monitored by TLC. The solvent was removed *in vacuo*. The residue was dissolved with H_2O (50 mL) and extracted with EA (3×50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was separated and purified using column chromatography on silica gel (EA:PE = 1:5) to obtain the compound **2a** (0.86 g, 80% yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.90 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.4, 2.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.47 (dd, J = 7.6, 5.2 Hz, 1H), 4.27 (s, 1H), 4.08-4.01 (m, 3H), 3.97 (q, J = 7.2 Hz, 2H), 1.41-1.24 (m, 9H). Compounds **3a**-**4a** and **8a**-**11a** were obtained with the same synthetic method as described in the preparation of **2a**.

To a stirred solution of **1e** (1.0 g, 2.88 mmol), PPh_3 (907 mg, 3.46 mmol) and oxetane-3-ol (219 μL, 3.46 mmol) in THF (15 mL) was added DEAD (545 μL, 3.46 mmol) slowly at 0 ℃ under N_2. Then, the mixture was stirred at 60 ℃ for 12 h. After the reaction was completed, monitored by TLC. The residue was dissolved with H_2O (50 mL) and extracted with EA (3×50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:5) to obtain the compound **5a** (0.58 g, 50% yield) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.91 (d, J = 2.4 Hz, 1H), 7.84 (dd, J = 8.4, 2.4 Hz, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.73 (d, J = 8.8 Hz, 2H), 5.47 (dd, J = 7.6, 5.2 Hz, 1H), 5.26-5.19 (m, 1H), 4.90 (t, J = 6.8 Hz, 2H), 4.55-4.49 (m, 2H), 4.27 (t, J = 8.0 Hz, 1H), 4.07 (s, 2H), 4.04 (dd, J = 8.4, 5.2 Hz, 1H), 1.36 (s, 3H), 1.29 (s, 3H). Compounds **6a**-**7a** were obtained with the same synthetic method as described in the preparation of **5a**.

A mixture of 3-bromopyridazine (1.0 g, 6.29 mmol), **1e** (2.62 g, 7.55 mmol), K_3PO_4 (4.01 g, 18.87 mmol), $Pd(OAc)_2$ (28 mg, 0.13 mmol) and *t*-BuXPhos (80 mg, 0.19 mmol) in toluene (10 mL) was stirred at 120 ℃ under N_2 for 16 h. After the reaction was completed, monitored by TLC. The solution cooled to room temperature, and then dissolved with H_2O (50 mL) and extracted with EA (3×50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:3) to obtain the compound **12a** (1.33 g, 50% yield) as a light brown liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.99 (dd, J = 4.4, 1.2 Hz, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.75 (dd, J = 8.8, 4.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.43 (dd, J = 9.2, 1.6 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.19-7.13 (m, 2H), 5.50 (dd, J = 7.6, 5.2 Hz, 1H), 4.29 (dd, J = 8.4, 7.6 Hz, 1H), 4.19 (s, 2H), 4.06 (dd, J = 8.4, 5.2 Hz, 1H), 1.37 (s, 3H), 1.31 (s, 3H). Compound **13a** was obtained with the same synthetic method as described in the preparation of **12a**.

General synthesis of compounds 02-13

Compounds **2a**-**13a** (0.3 mmol) were dissolved in anhydrous MeOH (5 mL), and HCl in H_2O (4 M, 0.23 mL, 0.9 mmol) was added slowly and the mixture was stirred at room temperature overnight. After the reaction was completed, monitored by TLC. The solution was concentrated *in vacuo*, and the residue was diluted with H_2O (25 mL) and extracted with DCM (3×25 mL). The organic layer was washed with saturated NaCl solution (25 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was

purified using column chromatography on silica gel to obtain compound **02-13**.

(*R*)-1-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2,3-dihydroxypropan-1-one (02)

Compound **02** was prepared according to the above general synthetic method as a white solid (55% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 2.0 Hz, 1H), 7.87 (dd, J = 8.4, 2.0 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.12 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.4 Hz, 2H), 5.35 (d, J = 6.4 Hz, 1H), 4.93 (q, J = 4.8 Hz, 1H), 4.83 (t, J = 6.0 Hz, 1H), 4.06 (s, 2H), 3.97 (q, J = 6.8 Hz, 2H), 3.72-3.58 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H). HRMS (ESI) m/z calcd for $C_{18}H_{19}ClO_4$ $[M+Cl]^-$ 369.0656, found 369.0666.

(*R*)-1-(4-chloro-3-(4-isopropoxybenzyl)phenyl)-2,3-dihydroxypropan-1-one (03)

Compound **03** was prepared according to the above general synthetic method as a light yellow solid (62% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.11 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 5.33 (d, J = 6.8 Hz, 1H), 4.92 (q, J = 4.8 Hz, 1H), 4.80 (t, J = 5.6 Hz, 1H), 4.58-4.50 (m, 1H), 4.05 (s, 2H), 3.71-3.58 (m, 2H), 1.23 (d, J = 6.0 Hz, 6H).(ESI) m/z calcd for $C_{19}H_{21}ClO_4$ $[M+Na]^+$ 371.1021, found 371.1027.

(*R*)-1-(4-chloro-3-(4-(cyclopentyloxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (04)

Compound **04** was prepared according to the above general synthetic method as a white solid (52% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.95 (dd, J = 16.4, 2.4 Hz, 1H), 7.91-7.85 (m, 1H), 7.60 (dd, J = 8.4, 5.6 Hz, 1H), 7.26 (d, J = 1.6 Hz, 1H), 7.13-7.05 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 5.35 (dd, J = 6.4, 4.8 Hz, 1H), 4.96-4.89 (m, 1H), 4.88-4.73 (m, 2H), 4.06 (d, J = 7.6 Hz, 2H), 3.71-3.57 (m, 2H), 1.94-1.82 (m, 2H), 1.75-1.63 (m, 4H), 1.62-1.52 (m, 2H). (ESI) m/z calcd for $C_{21}H_{23}ClO_4$ $[M+Na]^+$ 397.1177, found 397.1187.

(*R*)-1-(4-chloro-3-(4-(oxetan-3-yloxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (05)

Compound **05** was prepared according to the above general synthetic method as a white solid (37% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.72 (d, J = 8.8 Hz, 2H), 5.35 (d, J = 6.8 Hz, 1H), 5.23 (t, J = 6.0 Hz, 1H), 4.95-4.87 (m, 3H), 4.83 (t, J = 6.0 Hz, 1H), 4.52 (dd, J = 7.6, 5.2 Hz, 2H), 4.07 (s, 2H), 3.70-3.58 (m, 2H). HRMS (EI) m/z calcd for $C_{19}H_{19}ClO_5$ $[M]^+$ 361.0848, found 361.0840.

(*R*)-1-(4-chloro-3-(4-(((*R*)-tetrahydrofuran-3-yl)oxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (06)

Compound **06** was prepared according to the above general synthetic method as a

white solid (52% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.14 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 5.00-4.95 (m, 1H), 4.93 (t, J = 4.4 Hz, 1H), 4.07 (s, 2H), 3.81-3.77 (m, 3H), 3.77-3.72 (m, 2H), 3.71-3.59 (m, 3H), 2.24-2.13 (m, 1H), 1.97-1.89 (m, 1H). HRMS (ESI) m/z calcd for $C_{20}H_{21}ClO_5$ $[M+Na]^+$ 399.0970, found 399.0967.

(*R*)-1-(4-chloro-3-(4-((tetrahydro-2H-pyran-4-yl)oxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (07)

Compound **07** was prepared according to the above general synthetic method as a colorless liquid (24% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.13 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 5.36 (d, J = 6.4 Hz, 1H), 4.93 (q, J = 4.8 Hz, 1H), 4.84 (t, J = 6.0 Hz, 1H), 4.54-4.47 (m, 1H), 4.06 (s, 2H), 3.86-3.79 (m, 2H), 3.71-3.58 (m, 2H), 1.97-1.90 (m, 2H), 1.59-1.49 (m, 2H), 1.30-1.21 (m, 2H). HRMS (ESI) m/z calcd for $C_{21}H_{23}ClO_5$ $[M+Na]^+$ 413.1126, found 413.1130.

(*R*)-1-(3-(4-(benzyloxy)benzyl)-4-chlorophenyl)-2,3-dihydroxypropan-1-one (08)

Compound **08** was prepared according to the above general synthetic method as a white solid (66% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (d, J = 2.4 Hz, 1H), 7.88 (dd, J = 8.4, 2.4 Hz, 1H), 7.59 (d, J = 8.4 Hz, 1H), 7.43 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 6.8 Hz, 2H), 7.35-7.29 (m, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 5.37 (d, J = 6.4 Hz, 1H), 5.06 (s, 2H), 4.96-4.91 (m, 1H), 4.84 (t, J = 6.0 Hz, 1H), 4.07 (s, 2H), 3.72-3.58 (m, 2H). HRMS (ESI) m/z calcd for $C_{23}H_{21}ClO_4$ $[M+Na]^+$ 419.1021, found 419.1029.

(*R*)-1-(3-(4-([1,1'-biphenyl]-4-ylmethoxy)benzyl)-4-chlorophenyl)-2,3-dihydroxypropan-1-one (09)

Compound **09** was prepared according to the above general synthetic method as a white solid (63% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.93 (d, J = 2.4 Hz, 1H), 7.87 (dd, J = 8.4, 2.4 Hz, 1H), 7.70-7.64 (m, 4H), 7.59 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.2 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.97 (d, J = 8.4 Hz, 2H), 5.33 (s, 1H), 5.12 (s, 2H), 4.86 (d, J = 46.4 Hz, 2H), 4.07 (s, 2H), 3.72-3.57 (m, 2H). HRMS (ESI) m/z calcd for $C_{29}H_{25}ClO_4$ $[M+Na]^+$ 495.1334, found 495.1341.

(*R*)-1-(4-chloro-3-(4-(thiophen-3-ylmethoxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (10)

Compound **10** was prepared according to the above general synthetic method as a white solid (46% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.92 (d, J = 2.4 Hz, 1H),

7.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.19-7.11 (m, 3H), 6.94 (d, *J* = 8.4 Hz, 2H), 5.33 (d, *J* = 6.4 Hz, 1H), 5.04 (s, 2H), 4.92 (q, *J* = 5.2 Hz, 1H), 4.80 (t, *J* = 5.6 Hz, 1H), 4.07 (s, 2H), 3.70-3.58 (m, 2H). HRMS (ESI) m/z calcd for $C_{21}H_{19}ClO_4S$ $[M+Na]^+$ 425.0585, found 425.0584.

(*R*)-1-(4-chloro-3-(4-((2-chloro-5-methylpyrimidin-4-yl)oxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (11)

Compound **11** was prepared according to the above general synthetic method as a white solid (53% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 8.49 (d, *J* = 1.2 Hz, 1H), 8.03 (d, *J* = 2.4 Hz, 1H), 7.91 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.35 (d, *J* = 6.4 Hz, 1H), 4.94 (q, *J* = 5.2 Hz, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 4.20 (s, 2H), 3.74-3.58 (m, 2H), 2.25 (d, *J* = 0.8 Hz, 3H). HRMS (EI) m/z calcd for $C_{21}H_{18}Cl_2N_2O_4$ $[M]^+$ 431.0571, found 431.0562.

(*R*)-1-(4-chloro-3-(4-(pyridazin-3-yloxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (12)

Compound **12** was prepared according to the above general synthetic method as a white solid (64% yield). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.99 (dd, *J* = 3.2, 1.2 Hz, 1H), 8.03 (d, *J* = 1.8 Hz, 1H), 7.90 (dd, *J* = 8.4, 1.8 Hz, 1H), 7.75 (dd, *J* = 9.0, 4.8 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.43 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.16 (d, *J* = 9.0 Hz, 2H), 5.36 (d, *J* = 6.0 Hz, 1H), 4.96-4.92 (m, 1H), 4.82 (t, *J* = 6.0 Hz, 1H), 4.19 (s, 2H), 3.72-3.67 (m, 1H), 3.65-3.61 (m, 1H). HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_4$ $[M+H]^+$ 385.0950, found 385.0953.

(*R*)-1-(4-chloro-3-(4-(pyrimidin-2-yloxy)benzyl)phenyl)-2,3-dihydroxypropan-1-one (13)

Compound **13** was prepared according to the above general synthetic method as a white solid (55% yield). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 8.62 (d, *J* = 4.8 Hz, 2H), 8.04 (d, *J* = 2.4 Hz, 1H), 7.90 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.25 (t, *J* = 4.8 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 2H), 5.36 (d, *J* = 6.6 Hz, 1H), 4.96-4.93 (m, 1H), 4.82 (t, *J* = 6.0 Hz, 1H), 4.18 (s, 2H), 3.71-3.67 (m, 1H), 3.66-3.61 (m, 1H).HRMS (ESI) m/z calcd for $C_{20}H_{17}ClN_2O_4$ $[M+H]^+$ 385.0950, found 385.0953.

General synthesis of compounds 14a-20a

To a solution of 2-methylthiophene (1.0 g, 10.19 mmol) in THF (10 mL) was slowly added *n*-BuLi (7.64 mL,12.22 mmol) at -78 ℃ under N_2 and the mixture was stirred at -78 ℃ for 1 h. Then, 5-bromo-2-chlorobenzaldehyde (3.35 g, 15.28 mmol) was added to the solution and the mixture was stirred at room temperature for 12 h.

After the reaction was completed, monitored by TLC. The residue was dissolved with H_2O (50 mL) and extracted with EA (3×50 mL). The organic layer was washed with saturated NaCl solution (50 mL), dried with Na_2SO_4, concentrated *in vacuo* to obtain the compound **14a** (2.59 g, 80% yield) as a white solid. The crude product was used directly in the following steps without further purification. Compounds **15a-20a** were obtained with the same synthetic method as described in the preparation of **14a**.

General synthesis of compounds 14b-20b

To a solution of **14a** (2.59 g, 8.15 mmol) in DCM/MeCN (30 mL, 1:1) were slowly added Et_3SiH (1,90 g, 16.31 mmol) and $BF_3 \cdot Et_2O$ (2.31 g, 16.31 mmol) at -20 ℃. Then, the mixture was stirred at -20 ℃ for 2 h. After the reaction was completed, monitored by TLC. The solvent was quenched by ice water (75 mL), and extracted with EA (3×75 mL). The organic layer was washed with saturated NaCl solution (75 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:20) to obtain the compound **14b** (1.96 g, 80% yield) as a colorless liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.4 Hz, 1H), 7.32 (dd, J = 8.8, 2.4 Hz, 1H), 7.26 (t, J = 8.4 Hz, 1H), 6.65-6.59 (m, 2H), 4.17 (s, 2H), 2.46 (s, 3H). Compounds **15b-20b** were obtained with the same synthetic method as described in the preparation of **14b**.

General synthesis of compounds 14c-20c

To a solution of **14b** (1.96 g, 6.50 mmol) in THF (20 mL) was slowly added *n*-BuLi (457.87 mg, 7.15 mmol) at -78 ºC under N_2 and the mixture was stirred at -78 ℃ for 1h. Then, (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (1.02 g, 7.80 mmol) was added to the solution and the mixture was stirred at room temperature for 12 h. After the reaction was completed, monitored by TLC. The residue was dissolved with H_2O (75 mL) and extracted with EA (3×75 mL). The organic layer was washed with saturated NaCl solution (75 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (EA:PE = 1:20) to obtain the compound **14c** (1.83 g, 80% yield) as a colorless liquid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.34-7.26 (m, 2H), 7.19 (t, J = 10.0 Hz, 1H), 6.61-6.51 (m, 2H), 5.62-5.51 (m, 1H), 4.48-4.24 (m, 1H), 4.08 (s, 2H), 3.92-3.82 (m, 2H), 3.61-3.46 (m, 1H), 2.29 (s, 3H), 1.26-1.12 (m, 6H). Compounds **15c-20c** were obtained with the same synthetic method as described in the preparation of **14c**.

General synthesis of compounds 14d-20d

To a solution of **14c** (1.83 g, 5.19 mmol) in DCM (20 mL) was added Dess-Martin Periodinane (1.32 g, 3.12 mmol) at 0 ℃ and the mixture was stirred at room temperature

for 2 h. After the reaction was completed, monitored by TLC. The solution was filtered by diatomaceous earth and the filtrate was concentrated *in vacuo* to obtain the compound **14d** (1.63 g, 90% yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ7.98 (d, J = 2.4 Hz, 1H), 7.86 (dd, J = 8.4, 2.4 Hz, 1H), 7.63 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 3.2 Hz, 1H), 6.62 (dd, J = 3.2, 1.2 Hz, 1H), 5.47 (dd, J = 7.2, 5.2 Hz, 1H), 4.31-4.25 (m, 1H), 4.24 (s, 2H), 4.05 (dd, J = 8.4, 4.8 Hz, 1H), 2.36 (s, 3H), 1.37 (s, 3H), 1.30 (s, 3H). Compounds **15d-20d** were obtained with the same synthetic method as described in the preparation of **14d**.

General synthesis of compounds 14-20

Compounds **14d-20d** (0.3 mmol) were dissolved in anhydrous MeOH (5 mL), HCl in H_2O (4 M, 0.23 mL, 0.9 mmol) was added slowly and the mixture was stirred at room temperature overnight. After the reaction was completed, monitored by TLC. The solution was concentrated *in vacuo* and the residue was dissolved with H_2O (25 mL) and extracted with DCM (3×25 mL). The organic layer was washed with saturated NaCl solution (25 mL), dried with Na_2SO_4, concentrated *in vacuo* and the residue was purified using column chromatography on silica gel (DCM:MeOH = 20:1) to obtain compound **14-20**.

(*R*)-1-(4-chloro-3-((5-methylthiophen-2-yl)methyl)phenyl)-2,3-dihydroxypropan-1-one (14)

Compound **14** was prepared according to the above general synthetic method as a white solid (46% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.98 (d, J = 2.4 Hz, 1H), 7.89 (dd, J = 8.4, 2.4 Hz, 1H), 7.60 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 3.0 Hz, 1H), 6.63-6.59 (m, 1H), 5.35 (d, J = 6.6 Hz, 1H), 4.93-4.89 (m, 1H), 4.80 (t, J = 6.0 Hz, 1H), 4.23 (s, 2H), 3.70-3.66 (m, 1H), 3.64-3.60 (m, 1H), 2.35 (s, 3H). HRMS (EI) m/z calcd for $C_{15}H_{15}ClO_3S$ $[M]^+$ 310.0430, found 310.0435.

(*R*)-1-(4-chloro-3-(naphthalen-2-ylmethyl)phenyl)-2,3-dihydroxypropan-1-one (15)

Compound **15** was prepared according to the above general synthetic method as a colorless liquid (44% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.05 (d, J = 2.4 Hz, 1H), 7.93 (dd, J = 8.4, 2.4 Hz, 1H), 7.90-7.81 (m, 3H), 7.71 (s, 1H), 7.63 (d, J = 8.4 Hz, 1H), 7.52-7.44 (m, 2H), 7.41 (dd, J = 8.4, 1.6 Hz, 1H), 5.40 (d, J = 6.8 Hz, 1H), 4.98 (q, J = 4.8 Hz, 1H), 4.87 (t, J = 6.0 Hz, 1H), 4.33 (s, 2H), 3.77-3.63 (m, 2H).HRMS (ESI) m/z calcd for $C_{20}H_{17}ClO_3$ $[M+Na]^+$ 363.0758, found 363.0761.

(*R*)-1-(4-chloro-3-((2,3-dihydro-1H-inden-5-yl)methyl)phenyl)-2,3-dihydroxypropan-1-one (16)

Compound **16** was prepared according to the above general synthetic method as a white solid (49% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.95 (d, *J* = 2.4 Hz, 1H), 7.88 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.06 (s, 1H), 6.97 (d, *J* = 7.6 Hz, 1H), 5.35 (d, *J* = 6.4 Hz, 1H), 4.94 (q, *J* = 4.8 Hz, 1H), 4.82 (t, *J* = 5.6 Hz, 1H), 4.09 (s, 2H), 3.74-3.60 (m, 2H), 2.79 (t, *J* = 7.6 Hz, 4H), 2.02-1.92 (m, 2H). HRMS (ESI) m/z calcd for $C_{19}H_{19}ClO_3$ $[M+Na]^+$ 353.0915, found 353.0921.

(*R*)-1-(4-chloro-3-((5,6,7,8-tetrahydronaphthalen-2-yl)methyl)phenyl)-2,3-dihydroxypropan-1-one (17)

Compound **17** was prepared according to the above general synthetic method as a white solid (32% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.94 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 6.90 (d, *J* = 5.6 Hz, 2H), 5.33 (d, *J* = 6.8 Hz, 1H), 4.96-4.89 (m, 1H), 4.80 (t, *J* = 6.0 Hz, 1H), 4.05 (s, 2H), 3.73-3.58 (m, 2H), 2.65 (s, 4H), 1.75-1.64 (m, 4H). HRMS (ESI) m/z calcd for $C_{20}H_{21}ClO_3$ $[M+Na]^+$ 367.1071, found 367.1075.

(*R*)-1-(4-chloro-3-((2,3-dihydrobenzofuran-5-yl)methyl)phenyl)-2,3-dihydroxypropan-1-one (18)

Compound **18** was prepared according to the above general synthetic method as a colorless liquid (40% yield). ^{1}H NMR (400 MHz, DMSO-*d*$_6$) δ 7.93 (d, *J* = 2.4 Hz, 1H), 7.87 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.07 (s, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 5.34 (d, *J* = 6.4 Hz, 1H), 4.93 (q, *J* = 4.8 Hz, 1H), 4.81 (t, *J* = 5.6 Hz, 1H), 4.47 (t, *J* = 8.4 Hz, 2H), 4.04 (s, 2H), 3.73-3.58 (m, 2H), 3.12 (t, *J* = 8.7 Hz, 2H). HRMS (ESI) m/z calcd for $C_{18}H_{17}ClO_4$ $[M+Na]^+$ 355.0708, found 355.0714.

(*R*)-1-(3-(benzo[d][1,3]dioxol-5-ylmethyl)-4-chlorophenyl)-2,3-dihydroxypropan-1-one (19)

Compound **19** was prepared according to the above general synthetic method as a white solid (58% yield). ^{1}H NMR (600 MHz, DMSO-*d*$_6$) δ 7.93 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 6.80 (d, *J* = 1.2 Hz, 1H), 6.68 (dd, *J* = 7.8, 1.8 Hz, 1H), 5.97 (s, 2H), 5.33 (d, *J* = 6.0 Hz, 1H), 4.94-4.90 (m, 1H), 4.80 (t, *J* = 5.4 Hz, 1H), 4.05 (s, 2H), 3.70-3.65 (m, 1H), 3.64-3.59 (m, 1H). HRMS (ESI) m/z calcd for $C_{17}H_{15}ClO_5$ $[M+Na]^+$ 357.0500, found 357.0503.

(*R*)-1-(4-chloro-3-((2,3-dihydrobenzo[b][1,4]dioxin-6-yl)methyl)phenyl)-2,3-dihydroxypropan-1-one (20)

Compound **20** was prepared according to the above general synthetic method as a

white solid (53% yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.94 (s, 1H), 7.88 (d, J = 7.8 Hz, 1H), 7.58 (d, J = 8.4 Hz, 1H), 6.77 (d, J = 7.8 Hz, 1H), 6.72-6.65 (m, 2H), 5.34 (d, J = 6.0 Hz, 1H), 4.93 (q, J = 4.8 Hz, 1H), 4.81 (t, J = 5.4 Hz, 1H), 4.19 (s, 4H), 4.01 (s, 2H), 3.72-3.66 (m, 1H), 3.66-3.60 (m, 1H). HRMS (ESI) m/z calcd for $C_{18}H_{17}ClO_5$ $[M+Na]^+$ 371.0657, found 371.0664.

HPLC analysis data of compounds purity

Table S1. HPLC analysis method and data of compounds **01-20**

Equipment		Agilent 1100 with quaternary pump, diode-array detector (DAD)	
Column		Agilent Exlipse XDB-C18 (250×4.6 mm, 5 μm particle size)	
System condition		CH_3OH : H_2O = 90:10 (v/v) as eluent, flow rate: 0.5 mL/min	
Results	Compd.	Retention time (min)	Relative purity (%)
	01	6.749	98.43
	02	3.936	99.19
	03	3.884	99.23
	04	3.629	98.76
	05	8.512	95.18
	06	8.494	97.17
	07	3.648	98.62
	08	9.259	96.43
	09	12.357	97.38
	10	3.673	98.77
	11	3.200	99.80
	12	3.177	99.87
	13	3.215	98.86
	14	3.852	98.02
	15	8.624	99.07
	16	5.260	97.81
	17	5.270	98.49
	18	3.107	95.14
	19	7.596	97.14

	20	7.557	99.61

Cardioprotective effects of compounds 01-20

Table S2. Cardioprotective effects of compounds **01-20** in H9c2 cells

Compd.	Cell viability (% of control)			
	1 μM	10 μM	50 μM	100 μM
EMPA	44.7±2.6	**62.7±9.6^{ns}**	**66.3±1.4*****	43.2±4.1
JX22	**59.5±2.0****	**62.3±5.1***	**80.5±5.3*****	1.5±0.8
01	40.2±1.6	52.8±8.0	**81.1±5.8****	2.1±1.0
02	**59.1±3.1***	**60.8±1.1****	14.4±11.5	0.8±0.5
03	44.9±6.1	42.4±3.9	0.1±0.1	0.9±0.4
04	52.1±12.6	**56.1±1.3***	2.4±1.2	2.4±0.7
05	**54.2±4.3***	56.4±0.8	2.4±1.1	2.4±0.6
06	48.4±5.9	50.0±6.1	1.0±0.5	1.7±0.7
07	50.6±2.9	53.7±10.0	**70.3±7.5***	2.7±1.3
08	52.1±3.6	**62.8±3.5****	0.7±0.2	1.7±0.2
09	50.0±3.3	57.3±5.2	6.7±2.2	8.7±1.7
10	41.3±10.5	45.5±1.9	1.1±0.7	1.2±1.2
11	51.0±1.0	**67.1±1.9*****	9.3±4.9	2.3±0.3
12	52.0±4.4	**64.0±2.9****	**90.8±8.1****	38.2±5.9
13	53.5±4.9	51.0±1.7	**70.5±4.7****	36.3±20.4
14	38.3±0.9	44.6±0.9	2.2±1.2	1.7±1.2
15	46.4±2.5	54.4±1.7	32.5±8.0	1.1±0.1
16	38.9±3.3	49.2±3.9	1.7±1.2	1.4±0.2
17	47.3±8.0	54.5±14.6	1.3±0.5	1.5±1.4
18	**58.3±3.4***	52.6±7.5	**66.6±4.7****	22.7±9.2
19	45.5±5.0	39.3±1.9	56.4±3.0	50.2±1.0
20	45.6±4.5	37.8±2.2	56.7±3.6	52.7±3.1
DMSO	**50.6±2.1$^{####}$**			

The data are presented as the percentage of surviving cells relative to control cells and as the mean ± SD, n = 2-3. ####P < 0.0001 *vs.* control, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 *vs.* DMSO-treated group. Unpaired two-tailed Student's *t*-test.

Cytotoxicity of compounds JX22 and 12

Cultured human liver cell lines (HL7702) and human embryonic lung fibroblast (MRC5) were seeded at 10,000 cells per well in 96-well plates. After 24 h of seeding, the cells were exposed to various concentrations of compounds, the concentration was diluted in half down from 200 μM. After 48 h of incubation, the medium was removed, 10% CCK-8 solution was added to cells for incubation for 2 h, and OD value was detected at 450 nm. Based on the cell viability data, **12** displayed a wider safety range on both of two cell lines (**Fig. S1**).

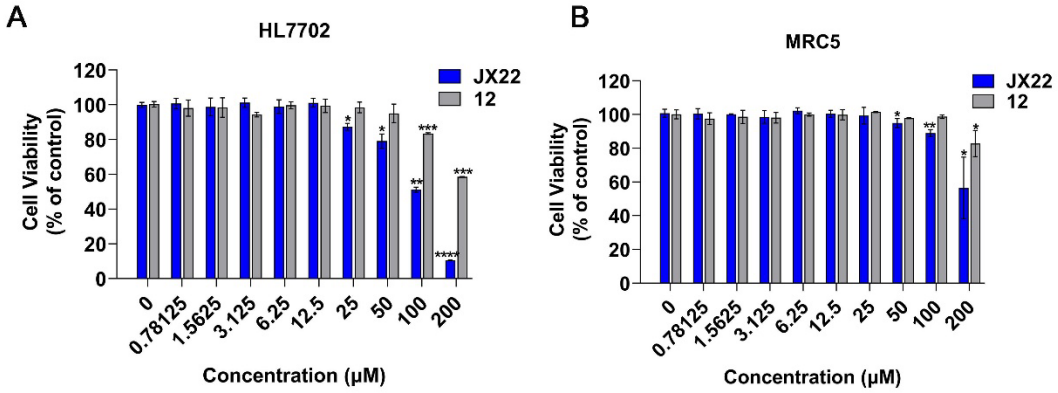

Figure S1 Cell viability of **JX22** and **12** in human cell lines. (A) Cell viability of **JX22** and **12** in HL7702 cells. (B) Cell viability of **JX22** and **12** in MRC5 cells. The data are shown as the mean ± SD, n = 2-3, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001.

Liver microsomal stability

Liver microsomal stability studies were commissioned by WuXi AppTec Co. Ltd. (Shanghai). For metabolic stability evaluation, pre-warm empty 'Incubation' plates T60 and NCF60 for 10 min minutes. Dilute liver microsomes to 0.56 mg/mL in 100 mM phosphate buffer. Transfer 445 μL microsome working solutions (0.56 mg/mL) into pre-warmed 'Incubation' plates T60 and NCF60, then pre-incubate 'Incubation' plates T60 and NCF60 for 10 min at 37 °C with constant shaking. Transfer 54 μL liver microsomes to blank plate, then add 6 μL NAPDH cofactor to blank plate, and then add 180 μL quenching solution to blank plate. Add 5 μL compound working solution (100 μM) into 'incubation' plates (T60 and NCF60) containing microsomes and mix 3 times thoroughly. For the NCF60 plate, add 50 uL of buffer and mix 3 times thoroughly. Start timing; plate will be incubated at 37 °C for 60 min while shaking. In 'Quenching' plate T0, add 180 μL quenching solution and 6 μL NAPDH cofactor. Ensure the plate is

chilled to prevent evaporation. For the T60 plate, mix 3 times thoroughly, and immediately remove 54 µL mixture for the 0-min time point to 'Quenching' plate. Then add 44 µL NAPDH cofactor to incubation plate (T60). Start timing, plate will be incubated at 37 °C for 60 min while shaking. At 5, 15, 30, 45, and 60 min, add 180 µL quenching solution to 'Quenching' plates, mix once, and serially transfer 60 µL sample from T60 plate per time point to 'Quenching' plates. For NCF60: mix once, and transfer 60 µL sample from the NCF60 incubation to 'Quenching' plate containing quenching solution at the 60−min time point. All sampling plates are shaken for 10 min, then centrifuged at 4000 rpm for 20 minutes at 4 °C. Transfer 80 µL supernatant into 240 µL HPLC water, and mix by plate shaker for 10 min. Each bioanalysis plate was sealed and shaken for 10 minutes prior to LC-MS/MS analysis.