Supplementary Material

Bioactivity-guided synthesis of tropine derivatives as new agonists for melatonin receptors

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1. Materials and instruments

The solvents were dried according to standard procedures. Organic solvents were analytical grade reagents, purchased from Tianjin Chemical Reagent Co., Ltd (Tianjin, China). All reaction were carried out under an Air atmosphere and monitored by using thin-layer chromatography (TLC, 200-300 mesh, Qingdao Makall Group Co., Ltd; Qingdao, China). Tropine and corresponding substituted acids were purchased from Alfa Aesar or J&K Scientific Ltd. ^{1}HNMR and ^{13}CNMR date were recorded in $CDCl_3$ on a 400 MHz spectrometer (Bruker, Bremerhaven, Germany) with tetramethylsilane (TMS) as the internal standard. Low-resolution mass spectra (MS) and high-resolution mass spectra (HRMS) data were measured on Shimadzu liquid chromatography-mass spectrometry (LCMS)-ion trap (IT)-time of flight (TOF) (Shimadzu, Kyoto, Japan). Flexstation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, California, USA).

2 Chemical Experimental Section

2.1 General procedure for preparation of compounds 1a-1l and 1n-1x

The *N,N*-dicyclohexylcarbodiimide (DCC, 1.2 equiv.) was dissolved in dry CH_2Cl_2 (5 mL). To a solution of the reduction product (2 mmol), appropriate carboxylic acid (1.2 equiv.) and 4-dimethylaminopyridine (DMAP, 0.2 equiv.) in anhydrous CH_2Cl_2 (5 mL), after stirred for 0.5 h at 0˚C, The mixture was slowly dropped the above solution of the DCC. The resulting solution was stirred for 24 h at room temperature monitored by TLC. The crude solution was filtered and washed with CH_2Cl_2 (2 × 10 mL), the solvent was removed under reduced pressure. The crude was dissolved in $CHCl_3$ (30 mL) and saturated NaCl (30 mL), neutralized with a solution of 5% NaOH. Then, extracted with $CHCl_3$ (3 × 30 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. Purification by column chromatography on silica gel ($CHCl_3$:MeOH: $CH_3CH_2NHCH_2CH_3$ = 92:6:2) to the target compound.

3*α*-Ethoxycarbonyltropane (1a). Yellow oil, yield 66%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.80 (t, 1H, *J* = 5.2 Hz, H-3), 3.02 (s, 2H, H-1, 5), 2.16 (s, 3H, *N*-CH_3), 2.06-2.01 (m, 2H, H-6, 7), 1.87 (s, 3H, CH_3CO), 1.86-1.80 (m, 4H, H-2, 4), 1.58-1.54 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.96 (s, CO), 66.80 (d, C-3), 59.74 (d, C-1, 5), 39.84 (s, C-8), 35.93 (t, C-2, 4), 25.21 (t, C-6, 7), 21.28 (q, COCH3). ESIMS: *m/z* 184 $[M + H]^+$, HRESIMS: calcd for $C_{10}H_{17}NO_2$ $[M + H]^+$ 184.1332, found 184.1308.

3*α*-Butyryloxy tropane (1b). Yellow oil, yield 64%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.89 (t, 1H, *J* = 5.2 Hz, H-3), 3.00 (s, 2H, H-1, 5), 2.17 (s, 3H, *N*-CH_3), 2.18-1.54 (m, 12H, H-2', 3', 2, 4, 6, 7), 0.86 (m, 3H, H-3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.54 (s, C-1'), 66.85 (d, C-3), 59.55 (d, C-1, 5), 40.15 (s, C-8), 36.63 (t, C-2'), 36.39 (t, C-2, 4), 25.36 (t, C-

6, 7), 18.17 (t, C-3'), 13.49 (q, C-4'). ESIMS: *m/z* 212 $[M + H]^+$, HRESIMS: calcd for $C_{12}H_{21}NO_2$ $[M + H]^+$ 212.1645,found 212.1565.

3*α*-(4'-Chlorobutyryloxy)tropane (1c). Yellow oil, yield 66%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.89 (t, 1H, *J* = 5.2 Hz, H-3), 3.35 (m, 1H, H-4'), 2.86 (s, 2H, H-1, 5), 3.35 (t, 1H, *J* = 7.2 Hz, H-2'), 2.02 (s, 3H, *N*-CH_3), 1.91-1.67 (m, 8H, H-3', 2, 4, 6, 7), 1.46-1.42 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 171.13 (s, C-1'), 67.00 (d, C-3), 59.18 (d, C-1, 5), 43.56 (t, C-4'), 39.75 (s, C-8), 35.90 (t, C-2, 4), 31.21 (t, C-2'), 27.03 (t, C-3'), 25.36 (t, C-6, 7). ESIMS: *m/z* 246 $[M + H]^+$, HRESIMS: calcd for $C_{12}H_{20}NO_2Cl$ $[M + H]^+$ 246.1255, found 246.1187.

3*α*-(2-Methylvaleryloxy)tropane (1d). Yellow oil, yield 64%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.89 (t, 1H, *J* = 5.2 Hz, H-3), 3.08 (s, 2H, H-1, 5), 2.40 (m, 1H, H-2'), 2.26 (s, 3H, *N*-CH_3), 2.14-1.90 (m, 8H, H-3', 2, 4, 6, 7), 1.66-1.61 (m, 4H, H-4', 6, 7), 1.29 (m, 3H, H-1''), 0.91 (m, 3H, H-5'). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 175.83 (s, C-1'), 66.78 (d, C-3), 59.72 (d, C-1, 5), 40.30 (s, C-8), 39.68 (d, C-2'), 36.57 (t, C-2, 4), 35.77 (t, C-3'), 25.51 (t, C-6, 7), 20.36 (t, C-4'), 16.84 (q, C-1''), 13.91 (q, C-5'). ESIMS: *m/z* 240 $[M + H]^+$, HRESIMS: calcd for $C_{14}H_{25}NO_2$ $[M + H]^+$ 240.1958, found 240.1875.

3*α*-(Myristoyloxy)tropane (1e). White amorphous powder, yield 64%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.95 (t, 1H, *J* = 5.2 Hz, H-3), 3.06 (s, 2H, H-1, 5), 2.26-2.22 (m, 2H, H-2'), 2.23 (s, 3H, *N*-CH_3), 2.10-1.88 (m, 8H, H-3', 2, 4, 6, 7), 1.66-1.57 (m, 4H, H-4', 6, 7), 1.66-1.57 (m, 4H, H-4', 6, 7), 1.26-1.22 (m, 18H, H-5', 6', 7', 8', 9', 10', 11', 12', 13'), 0.84 (m, 3H, H-14'). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.93 (s, C-1'), 67.00 (d, C-3), 59.69 (d, C-1, 5), 40.29 (s, C-8), 36.51 (t, C-2, 4), 34.87 (t, C-2'), 31.82 (t, C-12'), 29.57 (t, C-8'), 29.54 (t, C-7'), 29.49 (t, C-9'), 29.36 (t, C-6', 10'), 29.25 (t, C-11'), 29.16 (t, C-5'), 29.08 (t, C-4'), 25.55 (t, C-6, 7), 25.51 (t, C-3'), 22.59 (t, C-13'), 14.01 (q, C-14'). ESIMS: *m/z* 352 $[M + H]^+$, HRESIMS: calcd for $C_{22}H_{41}NO_2$ $[M + H]^+$ 352.3210, found 352.3179.

3*α*-(Benzoyloxy)tropane (1f). White amorphous powder, yield 63%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.85-7.83 (m, 2H, H-2'', 6''), 7.39-7.36 (m, 1H, H-4''), 7.28-7.25 (m, 2H, H-3'', 5''), 5.09 (t, 1H, *J* = 5.2 Hz, H-3), 3.03 (s, 2H, H-1, 5), 2.17 (s, 3H, *N*-CH_3), 2.15-2.07 (m, 2H, H-6, 7), 1.96-1.91 (m, 4H, H-2, 4), 1.68 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.41 (s, C-1'), 132.57 (d, C-4''), 130.37 (s, C-1''), 129.05 (d, C-2'', 6''), 128.13 (d, C-3'', 5''), 67.44 (d, C-3), 59.64 (d, C-1, 5), 39.95 (s, C-8), 36.13 (t, C-2, 4), 25.38 (t, C-6, 7). ESIMS: *m/z* 246 $[M + H]^+$, HRESIMS: calcd for $C_{15}H_{19}NO_2$ $[M + H]^+$ 246.1489, found 246.1468.

3*α*-(4''-Chlorobenzoyloxy)tropane (1g). White amorphous powder, yield 62%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.92-7.90 (m, 2H, H-2'', 6''), 7.39-7.37 (m, 2H, H-3'', 5''), 5.21 (t, 1H, *J* = 5.2 Hz, H-3), 3.12 (s, 2H, H-1, 5), 2.27 (s, 3H, *N*-CH_3), 2.26-1.97 (m, 6H, H-2, 4, 6, 7), 1.81-1.77 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.87 (s, C-1'), 139.15 (s, C-4''), 130.67 (d, C-2'', 6''), 129.15 (s, C-1''), 128.67 (d, C-3'', 5''), 68.37 (d, C-3), 59.63 (d, C-1, 5), 40.35

(s, C-8), 36.56 (t, C-2, 4), 25.71 (t, C-6, 7). ESIMS: *m/z* 280 $[M + H]^+$, HRESIMS: calcd for $C_{15}H_{18}NO_2Cl$ $[M + H]^+$ 280.1099, found 280.1050.

3*α*-(4''-Bromobenzoyloxy)tropane (1h). White amorphous powder, yield 64%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.83-7.81 (m, 2H, H-2'', 6''), 7.55-7.52 (m, 2H, H-3'', 5''), 5.19 (t, 1H, *J* = 5.2 Hz, H-3), 3.10 (s, 2H, H-1, 5), 2.25 (s, 3H, *N*-CH_3), 2.20-1.97 (m, 6H, H-2, 4, 6, 7), 1.79-1.75 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.89 (s, C-1'), 131.59 (d, C-2'', 6''), 130.59 (d, C-3'', 5''),129.50 (s, C-1''), 127.74 (s, C-1''), 68.28 (d, C-3), 59.92 (d, C-1, 5), 40.25 (s, C-8), 36.42 (t, C-2, 4), 25.61 (t, C-6, 7). ESIMS: *m/z* 324 $[M + H]^+$, HRESIMS: calcd for $C_{15}H_{18}NO_2Br$ $[M + H]^+$ 324.0594, found 324.0580.

3*α*-(Senecioyloxy)tropane (1i). Yellow oil, yield 63%, ^1H NMR ($CDCl_3$, 400 MHZ) δ_H: 5.52 (s, 1H, H-2'), 4.89 (t, 1H, *J* = 4.8 Hz, H-3), 2.96 (s, 2H, H-1, 5), 2.14 (s, 3H, *N*-CH_3), 2.04 (s, 3H, H-5'), 2.01-1.85 (m, 6H, H-2, 4, 6, 7), 1.76 (s, 3H, H-4'), 2.01-1.85 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.62 (s, C-1'), 156.03 (d, C-3'), 116.20 (d, C-2'), 67.29 (d, C-3), 59.55 (d, C-1, 5), 40.07 (s, C-8), 36.29 (t, C-2, 4), 27.01 (t, C-6, 7), 25.22 (q, C-5'), 19.76 (q, C-4'). ESIMS: *m/z* 224 $[M + H]^+$, HRESIMS: calcd for $C_{13}H_{21}NO_2$ $[M + H]^+$ 224.1645, found 224.1565.

3*α*-Cinnamoyloxytropane (1j). White amorphous powder, yield 67%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.64-7.60 (m, 1H, H-3'), 7.52-7.49 (m, 2H, H-2'', 6''), 7.36-7.26 (m, 3H, H-3'', 4'', 5''), 6.41-6.37 (m, 1H, H-2'), 5.09 (t, 1H, *J* = 5.2 Hz, H-3), 3.10 (s, 2H, H-1, 5), 2.26 (s, 3H, *N*-CH_3), 2.04-1.98 (m, 6H, H-2, 4, 6, 7), 1.78-1.74 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.18 (s, C-1'), 159.83 (s, C-3''), 144.33 (d, C-3'), 135.72 (s, C-1''), 129.85 (d, C-5''), 120.73 (d, C-6''), 119.10 (d, C-2'), 115.98 (d, C-4''), 115.98 (d, C-2''), 67.64 (d, C-3), 59.78 (d, C-1, 5), 55.28 (q, C-OMe), 40.43 (s, C-8), 36.60 (t, C-2, 4), 25.66 (t, C-6, 7).ESIMS: *m/z* 272 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{21}NO_2$ $[M + H]^+$ 272.1645, found 272.1582.

3*α*-(3'-Phenyl-propionyloxy)tropane (1k). White amorphous powder, yield 65%, ^1H NMR (400 MHz, $CDCl_3$) δ: 7.59-7.56 (m, 2H, H-2'', 6''), 7.44-7.42 (m, H, H-4''), 7.38-7.35 (m, 2H, H-3'', 5''), 5.11 (t, 1H, *J* = 5.3 Hz, H-3), 3.11 (s, 2H, H-1, 5), 2.27 (s, 3H, *N*-CH_3), 2.19-2.00 (m, 6H, H-2, 4, 6, 7), 1.83-1.79 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.63 (s, C-1'), 132.90 (d, C-2'', 6''), 130.50 (d, C-4''), 128.50 (d, C-3'', 5''), 119.67 (s, C-1''), 85.64 (s, C-3'), 81.04 (s, C-2'), 69.69 (d, C-3), 59.66 (d, C-1, 5), 40.28 (s, C-8), 36.43 (t, C-2, 4), 25.52 (t, C-6, 7). ESIMS: *m/z* 270 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{19}NO_2$ $[M + H]^+$ 270.1489, found 270.1421.

3*α*-(*N*-*tert*-butoxycarbonyl-*L*-glycine acyloxy)tropane (1l). White amorphous powder 61%, ^1H NMR ($CDCl_3$, 400 MHZ) δ_H: 7.26 (s, 1H, NH), 5.03 (t, 1H, *J* = 5.2 Hz, H-3), 3.86 (d, 1H, *J* = 5.6 Hz, H-2'), 3.07 (br, 2H, H-1, 5), 2.24 (s, 3H, *N*-CH_3), 2.15-1.85 (m, 6H, H-2, 4, 6, 7), 1.57 (m, 2H, H-6, 7), 1.43 (s, 9H, H-3'', 4'', 5''). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 169.58 (s, C-1'), 155.66 (s, C-1''), 79.94 (s, C-2''), 68.87 (d, C-3), 59.62 (d, C-1, 5), 42.79 (t, C-2'), 40.43 (s,

C-8), 36.55 (t, C-2, 4), 28.27 (q, C-3'', 4'', 5''), 25.55 (t, C-6, 7). ESIMS: m/z 299 [M + H] $^{+}$, HRESIMS: calcd for $C_{15}H_{26}N_2O_4$ [M + H]$^{+}$ 299.1965, found 299.1944.

3*α*-(2''-Methyl-cinnamoyloxy)tropane (1n). White amorphous powder, yield 63%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.83 (d, 1H, *J* = 16.0 Hz, H-3'), 7.44-7.43 (m, 1H, H-6''), 7.26-7.06 (m, 3H, H-3'', 4'', 5''), 7.10-6.99 (m, 2H, H-3'', 5''), 6.20 (d, 1H, *J* = 16.0 Hz, H-2'), 5.06 (t, 1H, *J* = 5.2 Hz, H-3), 3.57 (s, 2H, H-1, 5), 2.51(s, 3H, H-7''), 2.28 (s, 3H, *N*-CH_3), 2.55-2.10 (m, 6H, H-2, 4, 6, 7), 1.87-1.84 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.39 (s, C-1'), 142.57 (d, C-3'), 137.24 (s, C-1''), 132.52 (s, C-2''), 130.48 (d, C-4''), 129.97 (d, C-3''), 126.03 (d, C-6''), 125.91 (s, C-5''), 118.35 (d, C-2'), 67.97 (d, C-3), 60.18 (d, C-1, 5), 37.73 (s, C-8), 33.87 (t, C-2, 4), 24.46 (t, C-6, 7), 19.27 (d, C-7''). ESIMS: *m/z* 286 [M + H]$^{+}$, HRESIMS: calcd for $C_{18}H_{23}NO_2$ [M + H]$^{+}$ 286.1802, found 286.1746.

3*α*-(4''-Methyl--cinnamoyloxy)tropane (1o). White amorphous powder, yield 65%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.46 (d, 1H, *J* = 16.0 Hz, H-3'), 7.27-7.02 (m, 2H, H-2'', 3'', 5'', 6''), 6.20 (d, 1H, *J* = 16.0 Hz, H-2'), 5.01 (t, 1H, *J* = 5.2 Hz, H-3), 3.66 (s, 2H, H-1, 5), 2.57(s, 3H, H-7''), 2.20 (s, 3H, *N*-CH_3), 2.51-2.11 (m, 6H, H-2, 4, 6, 7), 1.88-1.84 (m, 2H, H-6, 7).^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.49 (s, C-1'), 145.07 (s, C-3'), 140.64 (d, C-4''), 130.74 (s, C-1''), 129.20 (d, C-3'', 5''), 127.70 (d, C-2'', 6''), 116.04 (d, C-2'), 64.45 (d, C-3), 60.59 (d, C-1, 5), 37.74 (s, C-8), 33.78 (t, C-2, 4), 24.13 (t, C-6, 7), 22.02 (d, C-7''). ESIMS: *m/z* 286 [M + H]$^{+}$, HRESIMS: calcd for $C_{18}H_{23}NO_2$ [M + H]$^{+}$ 286.1802, found 286.1745.

3*α*-(2''-Fluoro-cinnamoyloxy)tropane (1p). White amorphous powder, yield 64%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.70 (d, 1H, *J* = 16.0 Hz, H-3'), 7.49-7.45 (m, 1H, H-4''), 7.30-7.24 (m, 1H, H-6''), 7.10-6.99 (m, 2H, H-3'', 5''), 6.42 (d, 1H, *J* = 16.0 Hz, H-2'), 5.04 (t, 1H, *J* = 5.2 Hz, H-3), 3.05 (s, 2H, H-1, 5), 2.20 (s, 3H, *N*-CH_3), 2.12-1.90 (m, 6H, H-2, 4, 6, 7), 1.73-1.69 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.64 (s, C-1'), 164.01 (s, C-2''), 136.74 (d, C-3'), 131.53 (d, C-4''), 128.67 (d, C-6''), 124.25 (d, C-5''), 122.27 (s, C-1''), 116.04 (d, C-2'), 115.82 (d, C-3''), 67.56 (d, C-3), 59.58 (d, C-1, 5), 40.21 (s, C-8), 36.39 (t, C-2, 4), 25.45 (t, C-6, 7). ESIMS: *m/z* 290 [M + H]$^{+}$, HRESIMS: calcd for $C_{17}H_{20}NO_2F$ [M + H]$^{+}$ 290.1551, found 290.1501.

3*α*-(3''-Fluoro-cinnamoyloxy)tropane (1q). White amorphous powder, yield 68%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.52 (d, 1H, *J* = 16.0 Hz, H-3'), 7.31-7.15 (m, 3H, H-4'', 5'', 6''), 7.03-6.99 (m, 1H, H-2''), 6.42 (d, 1H, *J* = 16.0 Hz, H-2'), 5.04 (t, 1H, *J* = 5.2 Hz, H-3), 3.06 (s, 2H, H-1, 5), 2.22 (s, 3H, *N*-CH_3), 2.13-1.92 (m, 6H, H-2, 4, 6, 7), 1.73-1.70 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.64 (s, C-1'), 164.01 (s, C-3''), 142.84 (d, C-3'), 136.49 (s, C-1''), 130.28 (d, C-5''), 123.91 (d, C-6''), 120.05 (d, C-4''), 117.01 (d, C-2'), 114.18 (d, C-2''), 67.70 (d, C-3), 59.61 (d, C-1, 5), 40.28 (s, C-8), 36.46 (t, C-2, 4), 25.51 (t, C-6, 7). ESIMS: *m/z* 290 [M + H]$^{+}$, HRESIMS: calcd for $C_{17}H_{20}NO_2F$ [M + H]$^{+}$ 290.1551, found 290.1502.

3*α*-(4''-Fluoro-cinnamoyloxy)tropane (1r). White amorphous powder, yield 66%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.59 (d, 1H, *J* = 16.0 Hz, H-3'), 7.53-7.49 (m, 2H, H-2'', 6''), 7.09-7.04 (m, 2H, H-3'', 5''), 6.32 (d, 1H, *J* = 16.0 Hz, H-2'), 5.11 (t, 1H, *J* = 5.2 Hz, H-3), 3.16 (s, 2H, H-1, 5), 2.31 (s, 3H, *N*-CH_3), 2.23-1.95 (m, 6H, H-2, 4, 6, 7), 1.81-1.77 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.95 (s, C-1'), 164.99 (s, C-4''), 143.07 (d, C-3'), 130.50 (s, C-1''), 129.83 (d, C-2'', 6''), 118.40 (d, C-2'), 116.00 (d, C-3'', 5''), 67.42 (d, C-3), 59.73 (d, C-1, 5), 40.15 (s, C-8), 36.33 (t, C-2, 4), 25.51 (t, C-6, 7). ESIMS: *m/z* 290 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{20}NO_2F$ $[M + H]^+$ 290.1551, found 290.1514.

3*α*-(3''-Chloro-cinnamoyloxy)tropane (1s). White amorphous powder, yield 69%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.50 (d, 1H, *J* = 16.0 Hz, H-3'), 7.42-7.22 (m, 4H, H-2'', 4'', 5'', 6''), 6.32 (d, 1H, *J* = 16.0 Hz, H-2'), 5.09 (t, 1H, *J* = 5.2 Hz, H-3), 3.62 (s, 2H, H-1, 5), 2.56 (s, 3H, *N*-CH_3), 2.60-2.14 (m, 6H, H-2, 4, 6, 7), 1.92-1.88 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 165.20 (s, C-1'), 143.62 (d, C-3'), 135.65 (s, C-1''), 134.72 (s, C-3''), 130.23 (d, C-5''), 130.06 (d, C-4''), 127.55 (d, C-6''), 126.25 (d, C-2''), 119.08 (d, C-2'), 67.70 (d, C-3), 59.61 (d, C-1, 5), 40.28 (s, C-8), 36.46 (t, C-2, 4), 25.51 (t, C-6, 7). ESIMS: *m/z* 306 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{20}NO_2Cl$ $[M + H]^+$ 306.1255, found 306.1205.

3*α*-(3''-Methoxy-cinnamoyloxy)tropane (1t). White amorphous powder, yield 68%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.64-7.60 (m, 1H, H-3'), 7.33-7.29 (m, 1H, H-5''), 7.15-6.93 (m, 3H, H-2'', 4'', 6''), 6.42- 6.38 (m, 1H, H-2'), 5.13 (t, 1H, *J* = 5.2 Hz, H-3), 3.84 (s, 3H, OMe), 3.14 (s, 2H, H-1, 5), 2.30 (s, 3H, *N*-CH_3), 2.21-2.01 (m, 6H, H-2, 4, 6, 7), 1.81-1.78 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.11 (s, C-1'), 144.32 (s, C-3'), 134.28 (s, C-1''), 130.14 (d, C-3'', 5''), 128.76 (d, C-2'', 6''), 127.94 (d, C-4''), 118.74 (d, C-2'), 67.51 (d, C-3), 59.72 (d, C-1, 5), 40.34 (s, C-8), 36.52 (t, C-2, 4), 25.58 (t, C-6, 7). ESIMS: *m/z* 302 $[M + H]^+$, HRESIMS: calcd for $C_{18}H_{23}NO_3$ $[M + H]^+$ 302.1751, found 302.1711.

***tran*-3*α*-(2'',4''-Dichloro-cinnamoyloxy)tropane (1w).** White amorphous powder, yield 65 %, H NMR (400 MHz, $CDCl_3$) δ_H: 7.95 (d, 1H, *J* = 16.0 Hz, H-3'), 7.54-7.23 (m, 3H, H-3'', 5'', 6''), 6.34 (d, 1H, *J* = 16.0 Hz, H-2'), 5.17 (t, 1H, *J* = 5.2 Hz, H-3), 3.66 (s, 2H, H-1, 5), 2.60 (s, 3H, *N*-CH_3), 2.65-2.19 (m, 6H, H-2, 4, 6, 7), 1.96-1.92 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 164.81 (s, C-1'), 139.58 (d, C-3'), 136.54 (s, C-2''), 135.39 (s, C-1''),130.67 (s, C-4''), 129.88 (d, C-6''), 128.14 (d, C-3''), 127.52 (d, C-5''), 120.71 (d, C-2'), 65.64(d, C-3), 60.31 (d, C-1, 5),38.00 (s, C-8), 34.13 (t, C-2, 4),24.75 (t, C-6, 7). ESIMS: *m/z* 340 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{19}NO_2Cl_2$ $[M + H]^+$ 340.0866, found 340.0835.

3*α*-(3'',4''-Dimethoxy-cinnamoyloxy)tropane (1x). White amorphous powder, yield 63%, H NMR (400 MHz, $CDCl_3$) δ_H: 7.52 (d, 2H, *J* =15.9 Hz, H-3'), 7.20 (s, 1H, H-2''), 7.05 (dd, H, *J* = 8.3 Hz, 1.9 Hz, H-6''), 6.98 (dd, H, *J* = 8.3 Hz,

1.9 Hz, H-5''), 6.20 (d, 2H, *J* =15.9 Hz, H-3'), 5.04 (t, 1H, *J* = 5.2 Hz, H-3), 3.84 (s, 6H, H-OMe), 3.08 (s, 2H, H-1, 5), 2.25 (s, 3H, *N*-CH_3), 2.18-1.90 (m, 6H, H-2, 4, 6, 7), 1.68 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.43 (s, C-1'), 151.00 (s, C-3''), 149.09 (s, C-4''), 144.36 (d, C-3'), 127.24 (s, C-1''), 122.59 (d, C-6''), 116.33 (d, C-2'), 110.87 (d, C-5''), 109.41 (d, C-2''), 67.24 (d, C-3), 59.83 (d, C-1, 5), 55.85 (q, C-OMe), 40.26 (s, C-8), 36.43 (t, C-2, 4), 25.59 (t, C-6, 7). ESIMS: *m/z* 332 $[M + H]^+$, HRESIMS: calcd for $C_{19}H_{25}NO_4$ $[M + H]^+$ 332.1856, found 332.1834.

2.2. General procedure for preparation of compound 1m.

Piperazine (1.6 mmol) and compound **1c** (0.5 mmol) were dissolved in CH_3CN (10 mL), and the solution was heated to reflux for 6 h. After reaction, the solvent was removed under reduced pressure. The crude was dissolved in $CHCl_3$ (30 mL) and saturated NaCl (30 mL), extracted with $CHCl_3$ (3 × 30 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. Purification by column chromatography on silica gel ($CHCl_3$:MeOH:$CH_3CH_2NHCH_2CH_3$ = 91:7:2) to the compound **1m**.

3*α*-*N*-(4'-Piperidylbutyryloxy)tropane (1m). White amorphous powder, yield 95%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 4.94 (t, 1H, *J* = 5.2 Hz, H-3), 3.06 (s, 2H, H-1, 5), 2.57 -2.26 (m, 8H, H-2', 4', 2'', 6''), 2.24 (s, 3H, *N*-CH_3), 1.98-1.79 (m, 6H, H-2, 4, 6, 7), 1.68-1.64 (m, 2H, H-6, 7), 1.57-1.52 (m, 2H, H-3'), 1.35-0.81 (m, 6H, H-3'', 4'', 5''). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.77 (s, C-1'), 67.23 (d, C-3), 59.70 (d, C-1, 5), 58.47 (t, C-3'), 54.47 (t, C-2'', 6''), 40.33 (s, C-8), 36.51 (t, C-2, 4), 32.97 (t, C-2'), 25.86 (t, C-3'', 5''), 25.56 (t, C-6, 7), 24.36 (t, C-4''), 22.56 (t, C-3'). ESIMS: m/z 295 $[M + H]^+$, HRESIMS: calcd for $C_{17}H_{30}N_2O_2$ $[M + H]^+$ 295.2380, found 295.2345.

2.3 General procedure for preparation of derivative 2.

The pyridinium chlorochromate (PCC, 1.5 equiv) was dissolved in dry CH_2Cl_2 (5 mL). A solution of tropine (1 equiv) in dry CH_2Cl_2(5 mL) was added the above solution of the PCC in a dropwise manner at ultralow temperatures, The reaction mixture was allowed to stir at ultralow temperatures for 8h. Then, the solution was filtered, extracted with $CHCl_3$ (3 × 30 mL) and saturated NaCl (30 mL), the organic layer was dried over anhydrous Na_2SO_4 and concentrated to dryness under reduced pressure. Purification by column chromatography on silica gel ($CHCl_3$:MeOH:$CH_3CH_2NHCH_2CH_3$ = 92:6:2) to the target compound **2**.

Tropinone (2). The known compound[1]. White amorphous powder, yield 46%, ^{1}H NMR ($CDCl_3$, 400 MHZ) δ_H: 3.28 (s, 2H, H-1, 5), 2.55-2.50 (m, 2H, H-2, 4), 2.32 (s, 3H, *N*-CH_3), 2.04-1.94(m, 4H, H-2, 4, 6, 7), 1.45-1.43 (m, 2H, H-6, 7). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 209.28 (s, C-3), 60.39 (d, C-1,5), 47.20 (t, C-2,4), 37.97 (q, C-8), 27.35 (t, C-6, 7).

3. *In vitro* agonist activity

MT_1 (or MT_2)-expressing cell line was made in the HEK 293-Gα15 host cells, which supported high levels of recombinant MT_1 (or MT_2) expression on the cell surface and contained high levels of the promiscuous G protein

Gα15 to enhance coupling of the receptor to the calcium signaling pathway. The Fluo-8 Calcium Assay Kit from HDB provides a fast, simple and reliable fluorescence-based assay for detecting changes in intracellular calcium. With this kit, calcium assays on fluorometric plate reader become a mix-and-read procedure in which cells are incubated with the kit reagents for one hour and transferred directly to plate reader for evaluation.

HEK293 cell lines stably expressing the human melatonin MT_1 or MT_2 receptor was grown in Dubecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum (FBS), and cultured with 95% O_2/5% CO_2 at 37℃. The cells were seeded in a Matrigel coated 96-well black-wall bottom plate with a plating volume of 100 µL / well at a density of 4×104/well, and incubated in CO_2 incubator (Thermo Forma 3310, US) for overnight. Then the cells were dyed by HDB Wash Free Calcium Assay Kit, and placed in CO_2 incubator for 1h. Tested compounds and positive drug were dissolved in 10 µL dimethyl sulfoxide (DMSO) and 990 µL HBSS Buffer respectively, and extracted a plating volume of 100 µL/well in a Matrigel coated 96-well clear bottom plate. The absorption values were readed by Flexstation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, California, USA) at room temperature with wavelength (Excitation: 485 nm; Emissiom: 525 nm; Emission cut-off: 515 nm). The absorption values were readed by Flexstation 3 Benchtop Multi-Mode Microplate Reader (Molecular Devices, Sunnyvale, California, USA) at room temperature with wavelength (Excitation: 485 nm; Emissiom: 525 nm; Emission cut-off: 515 nm). The agonistic activities expressed as $\bar{X}$ ± SD (n = 3) were obtained by comparing to the highest agonistic activity that was achieved for melatonin at the highest concentration and was set as 100%. The results were calculated by the software of Graphpad Prism 5.0.

References and notes

1. W. H Chiou, Y. M. Chiang, G. T. Chen. *Tetrahedron-asymmetry.* **2014**, *25*, 92.