Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Supporting Information

Improved synthesis of 4-/6-substituted 2-carboxy-1*H*-indole-3-propionic acid derivatives and structure-activity relationships as GPR17 agonists

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Analytical data of the *di*–ethyl ester indole derivatives (9a–j):

Ethyl 4,6-dichloro-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9a):

^{1}H-NMR (DMSO–d_6): δ 1.14, 1.34 (each t, 3 H, ^{3}J = 7.1 Hz, CH_3); 2.55 (m, 2 H, 2′-H); 3.52 (m, 2 H, 1′-H); 4.04, 4.34 (each q, 2 H, ^{4}J = 7.1 Hz, CH_2); 7.15 (d, 1 H, J = 1.8 Hz, 5-H); 7.40 (d, 1 H, J = 1.8 Hz, 7-H), 12.05 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.14, 14.17 ($2CH_3$, each C=OOCH$_2$*CH$_3$*); 20.3 (C-2′); 35.0 (C-1′); 59.9, 60.9 $2CH_2$, each C=OO*CH$_2$*CH$_3$); 111.5 (C-7); 120.9 (C-4); 121.2 (C6); 122.1 (C-3), 125.7 (C-2); 127.4 (C-3a); 129.0 (C-5); 137.5 (C-7a); 161.05 (2′-CO_2Et); 171.96 (2-CO_2Et). LC-MS (*m/z*): 375 [M+NH_4^+]$^+$; 358 [M] $^+$; 356 [M]$^-$. Purity (LC-MS): 95.1%.

Ethyl 4,6-dibromo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9b):

^{1}H-NMR (DMSO–d_6): δ 1.15, 1.34 (each t, 3 H, ^{3}J = 7.1 Hz, CH_3); 2.55 (t, 2 H, ^{4}J = 8.2 Hz, 2′-H); 3.54 (t, 2 H, ^{4}J = 8.2 Hz, 1′-H); 4.05, 4.35 (each q, 2 H, J = 7.1 Hz, CH_2); 7.42 (d, 1 H, ^{4}J = 1 Hz, 5-H); 7.60 (d, 1 H, ^{4}J = 1 Hz, 7-H); 12.06 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6): δ 14.17, 14.20 ($2CH_3$, each C=OOCH$_2$*CH$_3$*); 19.9 (C-2′); 36.0 (C-1′); 59.9, 60.9 ($2CH_2$, each C=OO*CH$_2$*CH$_3$); 114.9 (C-7); 115.5 (C-4); 117.1 (C-6); 121.6 (C-3); 123.5 (C-2); 125.7 (C-3a); 126.4 (C-5); 138.0 (C-7a); 161.1 (2′-CO_2Et); 171.9 (2-CO_2Et). LC-MS (*m/z*): 465 [M+NH_4^+]$^+$, 448 [M]$^+$, 446 [M]$^-$. Purity (LC-MS): 98.2 %.

Ethyl 4,6-diiodo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9c):

^{1}H-NMR (DMSO–d_6) δ 1.17, 1.34 (each t, 3 H, ^{3}J = 7.1 Hz, CH_3); 2.55 (m, 2 H, 2′-H); 3.53 (m, 2 H, 1′-H); 4.06, 4.34 (each q, 2 H, ^{4}J = 7.1 Hz, CH_2); 7.80 (d, 2 H, J = 1.7 Hz, 5-H, 7-H), 11.91 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.2 ($2CH_3$, each C=OOCH$_2$*CH$_3$*); 19.1 (C-2′); 36.1 (C-1′); 59.9, 60.9 ($2CH_2$, each C=OO*CH$_2$*CH$_3$); 88.3 (C-4); 90.0 (C-6); 121.5 (C-7);

122.1 (C-3); 125.4 (C-2); 126.0 (C-3a); 137.9 (C-7a); 138.4 (C-5); 161.1 (2′-CO_2Et); 171.9 (2-CO_2Et). LC-MS (*m/z*): 542 $[M]^+$, 559 $[M+NH_4^+]^+$, 540 $[M]^-$. Purity (LC-MS): 98.1 %.

Ethyl 4,6-dimethoxy-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9d):

^{1}H-NMR (500 MHz, DMSO–d_6) δ 1.15, 1.31 (2 t, each 3 H, ^3J = 7.1 Hz, 2 CH_3), 2.49 (t, 2 H, ^3J = 7.8 Hz, H-1'), 3.38 (t, 2 H, ^3J = 8.0 Hz, H-2'), 3.75, 3.82 (2 s, each 3 H, OCH_3) 4.03, 4.28 (2 q, each 2 H, ^3J = 7.1 Hz, 2 CH_2), 6.13 (d, 1 H, ^4J = 2.0 Hz, H-5), 6.42 (d, 1 H, ^4J = 2.0 Hz, H-7), 11.28 (s, 1 H, NH). ^{13}C-NMR (125 MHz, DMSO–d_6) δ 14.2, 14.4 (2 CH_3, $CO_2CH_2\mathit{CH_3}$), 21.5 (C-1'), 35.9 (C-2'), 55.4, 55.5 (2 C, $O\mathit{CH_3}$), 59.8, 60.0 (2 CH_2, $CO_2\mathit{CH_2}CH_3$), 86.7 (C-5), 92.3 (C-7), 112.3 (C-3a), 121.0 (C-3), 122.8 (C-2), 138.5 (C-7a), 155.9 (C-4), 159.4 (C-6), 161.5, 172.5 (2 C, $\mathit{C}O_2$Et). Elemental Analysis for $C_{18}H_{23}NO_6$: Calcd.: C 61.88; H 6.64; N 4.01; O 27.48; found: C 62.47; H 6.42; N 4.13. LC-MS (*m/z*): 367.21 $[M+NH_4]^+$, 350.18 $[M]^+$, 348.18 $[M]^-$. Purity (LC-MS): 97.2%.

Ethyl 4,6-di(trifluoromethyl)-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9e):

^{1}H-NMR (DMSO–d_6): δ 1.17, 1.36 (each t, 3 H, ^3J = 7.1 Hz, CH_3); 2.49 (m, 2 H, 2'-H); 3.33 (m, 2 H, 1'-H); 4.07, 4.40 (each q, 2 H, ^4J = 7.1 Hz, CH_2); 7.68 (s, 1 H, 5-H); 8.07 (s, 1 H, 7-H); 12.76 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.1, 14.2 (2CH_3, each C=OO$CH_2\mathit{CH_3}$); 20.1 (C-2'), 34.8 (C-1'); 59.9, 61.4 (2CH_2, each C=OO$\mathit{CH_2}CH_3$); 114.6 (C-4); 115.2 (C-6); 119.5 (C-7); 120.9, 121.8, 122.1, 122.3 (CF_3-C-4); 122.7 (C-2); 123.1 (C-3); 123.3 (C-3a); 123.5, 123.8, 124.9, 125.2 (CF_3-C-6); 129.1 (C-5); 136.2 (C-7a); 160.7 (2'-CO_2Et); 172.0 (2-CO_2Et). LC-MS (*m/z*): 443 $[M+NH_4^+]^+$, 426 $[M]^+$, 424 $[M]^-$. Purity (LC-MS): 95.9%.

Ethyl 4,6-dichloro-5-fluoro-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9f):

^{1}H-NMR (DMSO–d_6) δ 1.14, 1.34 (each t, 3 H, ^3J = 7.1 Hz, CH_3); 2.54 (m, 2 H, 2′-H); 3.48 (m, 2 H, 1′-H); 4.04, 4.35 (each q, 2 H, ^4J = 7.1 Hz, CH_2); 7.50 (d, 1 H, ^2J = 6 Hz, 7-H); 12.08

(s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.1 (2CH_3, each C=OOCH_2*CH_3*); 20.1 (C-2′); 35.9 (C-1′); 59.9, 61.0 (2CH_2, each C=OO*CH_2*CH_3); 112.6 (C-7); 113.0, 113.2, 117.9, 188.1, 121.4, 121.5 (C-5); 122.1 (C-4); 126.8 (C-6); 132.7 (C-3); 147.3 (C-3a); 149.1 (C-2); 160.9 (2′-CO_2Et), 171.9 (2-CO_2Et). LC-MS (*m/z*): 377 [M+NH_4^+]$^+$, 360 [M]$^+$, 358 [M]$^-$. Purity (LC-MS): 96.3%.

Ethyl 4-bromo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9g):

^{1}H-NMR (DMSO–d_6) δ 1.16, 1.34 (each t, 3 H, ^3J = 7.1 Hz, CH_3); 2.57 (m, 2 H, 2′-H); 3.58 (m, 2 H, 1′-H); 4.06, 4.34 (each q, 2 H, ^4J = 7.1 Hz, CH_2); 7.13 (dd, 1 H, *J* = 7.5 Hz, 6-H); 7.27 (dd, 1 H, *J* = 1.75 Hz, 5-H); 7.45 (dd, 1 H, *J* = 1.8 Hz, 7-H); 11.94 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.20, 14.21 (2CH_3, each C=OOCH_2*CH_3*); 20.1 (C-2′); 36.2 (C-1′); 59.9, 60.7 (2CH_2, each C=OO*CH_2*CH_3), 112.6 (C-7); 114.5 (C-4); 121.3 (C-3); 124.2 (C-5); 124.5 (C-6); 125.0 (C-3a); 125.7 (C-2); 137.8 (C-7a); 161.4 (2′-CO_2Et); 172.1 (2-CO_2Et). LC-MS (*m/z*): 387 [M+NH_4^+]$^+$, 370 [M]$^+$, 368 [M]$^-$. Purity (LC-MS): 98.9%.

Ethyl 6-bromo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9h):

^{1}H-NMR (DMSO–d_6) δ 1.09,1.34 (each t, 3 H, ^3J = 7.1 Hz, CH_3); 2.57 (m, 2 H, 2′-H); 3.27 (m, 2 H, 1′-H); 3.98, 4.34 (each q, 2 H, ^4J = 7.1 Hz, CH_2); 7.18 (dd, 1 H, *J* = 1.8 Hz, 5-H); 7.56 (dd, 1 H, *J* = 1.8 Hz, 7-H); 7.64 (dd, 1 H, *J* = 8.5 Hz, 4-H); 11.69 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.10, 14.25 (2CH_3, each C=OOCH_2*CH_3*); 19.9 (C-2′); 35.0 (C-1′); 59.9, 60.6 (2CH_2, each C=OO*CH_2*CH_3); 114.9 (C-7), 117.9 (C-4), 121.7 (C-3), 122.5 (C-6), 122.7 (C-5), 124.2 (C-2) 126.0 (C-3a) 136.9 (C-7a), 161.39 (2′-CO_2Et), 172.29 (2-CO_2Et). LC-MS (*m/z*): 387 [M+NH_4^+]$^+$, 370 [M]$^+$, 368 [M]$^-$. Purity (LC-MS): 97.1%.

Ethyl 4-iodo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9i):

^{1}H- NMR (DMSO–d_6) δ 1.17, 1.34 (each t, 3 H, ^{3}J = 7.1 Hz, CH_3); 2.57 (m, 2 H, 2′-H); 3.58 (m, 2 H, 1′-H); 4.07, 4.34 (each q, 2 H, ^{4}J = 7 Hz, CH_2); 6.96 (t, 1 H, J = 8 Hz, 6-H); 7.48 (d, 1 H, J = 8.2 Hz, 5-H); 7.57 (d, 1 H, J = 8.2 Hz, 7-H); 11.86 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.2 ($2CH_3$, each C=OOCH$_2$*CH$_3$*); 19.1 (C-2′); 36.3 (C-1′); 59.9, 60.7 ($2CH_2$, each C=OO*CH$_2$*CH$_3$); 86.3 (C-4); 113.2 (C-7); 121.8 (C-3); 125.1 (C-3a); 126.2 (C-6); 126.3 (C-2); 132.0 (C-5); 137.2 (C-7a); 161.4 (2′-CO_2Et); 172.0 (2-CO_2Et). LC-MS (*m*/*z*): 433 $[M+NH_4^+]^+$, 416 $[M]^+$, 414 $[M]^-$. Purity (LC-MS): 100%.

Ethyl 6-iodo-3-(3-ethoxy-3-oxopropyl)-1*H*-indole-2-carboxylate (9j):

^{1}H- NMR (DMSO–d_6) δ 1.09, 1.34 (each t, 3 H, ^{3}J = 7 Hz, CH_3); 2.56 (m, 2 H, 2′-H); 3.25 (m, 2 H, 1′-H), 3.98, 4.34 (each q, 2 H, ^{4}J = 7 Hz, CH_2); 7.33 (dd, 1 H, J = 1.8 Hz, 5-H); 7.50 (d, 1 H, J = 8.5 Hz, 4-H); 7.77 (d, 1 H, J = 1.8 Hz, 7-H); 11.66 (s, 1 H, NH). ^{13}C-NMR (DMSO–d_6) δ 14.1, 14.3 ($2CH_3$, each C=OOCH$_2$*CH$_3$*); 19.9 (C-2′), 34.95 (C-1′); 59.9, 60.6 ($2CH_2$, each C=OO*CH$_2$*CH$_3$); 90.03(C-6), 121.0 (C-7); 121.7 (C-3); 122.6 (C-4); 123.7 (C-2); 126.3 (C-3a); 128.1 (C5); 137.5 (C-7a); 161.4 (2′-CO_2Et), 172.3 (2-CO_2Et). LC-MS (*m*/*z*): 433 $[M+NH_4^+]^+$, 416 $[M]^+$, 414 $[M]^-$. Purity (LC-MS): 98.2%.