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Supporting Information

Potency and Selectivity Optimization of Tryptophanol-Derived Oxazoloisoindolinones: Novel p53 Activators in Human Colorectal Cancer

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Supporting Information

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(3*S*,9b*R*)-9b-methyl-3-((1-methyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 2. Following the general procedure for *N*-methylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **1** (0.10 g, 0.32 mmol) in 2 mL of dimethylformamide, sodium hydride (0.015 g, 0.64 mmol) and methyl iodide (0.040 mL, 0.64 mmol) were added. Reaction time: 1.5 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.096 g, 90%). Mp: 168-170 °C; $[\alpha]^{20}_D$ = +10.8° (c = 0.46, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.1, 1H, ArH), 7.72 (d, *J* = 7.8 Hz, 1H, ArH), 7.64 – 7.58 (m, 1H, ArH), 7.54 (s, 1H, ArH), 7.51 (dd, *J* = 7.1, 1.2 Hz, 1H, ArH), 7.31 (d, *J* = 8.1 Hz, 1H, ArH), 7.25 (dt, *J* = 6.8, 1.0 Hz, 1H, ArCH), 7.15 (dt, J = 7.9, 1.2 Hz 1H, ArH), 7.11 (s, 1H, ArH), 4.63 – 4.53 (m, 1H, H-3), 4.30 (dd, *J* = 8.8, 7.4 Hz, 1H, H-2), 4.17 (dd, *J* = 8.9, 6.3 Hz, 1H, H-2), 3.78 (s, 3H, *N*-CH_3), 3.44 (dd, *J* = 14.8, 5.6 Hz, 1H, CH_2-indole), 3.15 (dd, *J* = 14.7, 8.9 Hz, 1H, CH_2-indole), 1.72 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.49 (C=O), 147.55 (Cq), 137.08 (Cq), 133.32 (ArCH), 131.84 (Cq), 130.25 (ArCH), 128.23 (Cq), 127.32 (ArCH), 124.42 (ArCH), 122.23 (ArCH), 121.88 (ArCH), 119.19 (ArCH), 119.12 (ArCH), 110.33 (Cq), 109.37 (ArCH), 99.09 (C-9b), 74.92 (C-2), 56.34 (C-3), 32.85 (*N*-CH_3), 30.79 (CH_2-indole), 23.34 (CH_3). MS (ESI) m/z calcd for $C_{21}H_{20}N_2O_2$: 332.2, found 333.3 $[M+H]^+$.

(3*S*,9b*R*)-9b-methyl-3-((1-ethyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 3. Following the general procedure for *N*-ethylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **1** (0.051 g, 0.16 mmol) in 2 mL of dimethylformamide, sodium hydride (0.008 g, 0.32 mmol) and ethyl iodide (0.025 mL, 0.31 mmol) were added. Reaction time: 2 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white crystalline solid (0.040 g, 72%). Mp: 161-163 °C; $[\alpha]^{20}_D$ = +24.7° (c = 0.39, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.7 Hz, 1H, ArH), 7.72 (d, *J* = 7.8 Hz, 1H, ArH), 7.61 (m, 1H, ArH), 7.52 (dd, *J* = 7.3, 6.3 Hz, 2H, ArH), 7.34 (d, *J* = 8.1 Hz, 1H, ArH), 7.23 (t, *J* = 7.7 Hz, 1H, ArH), 7.18 (s, 1H, ArH), 7.14 (t, *J* = 7.8 Hz, 1H, ArH), 4.63 – 4.52 (m, 1H, H-3), 4.30 (dd, *J* = 8.85, 7.35 Hz, 1H, H-2), 4.16 (q, *J* = 7.24 Hz, 3H, H-2, *N*-CH_2), 3.43 (dd, *J* = 14.7, 5.3 Hz, 1H, CH_2-indole), 3.17 (dd, *J* = 14.7, 8.8 Hz, 1H, CH_2-indole), 1.68 (s, 1H, CH_3), 1.46 (t, *J* = 7.3 Hz, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.50 (C=O), 147.49 (Cq), 136.04 (Cq), 133.30 (ArCH), 131.83 (Cq), 130.25 (ArCH), 128.36 (Cq), 125.60 (ArCH), 124.40 (ArCH), 122.22 (ArCH), 121.71 (ArCH), 119.22 (ArCH), 119.12 (ArCH), 110.32 (Cq), 109.43 (ArCH), 99.07 (C-9b), 74.85 (C-2), 56.33 (C-3), 40.96 (*N*-CH_2), 30.70 (CH_2-indole), 23.25 (CH_3), 15.66 ($CH_2\underline{C}H_3$). Anal. Calc. ($C_{22}H_{22}N_2O_2$): C 76.28%; H 6.40%; N 8.09%. Found C 76.34%; H 6.50%; N 8.08%.

(3*S*,9b*R*)-9b-methyl-3-((1-propyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 4. Following the general procedure for *N*-propylation, to a stirred solution of derivative **1** (0.106 g, 0.33 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0151 g, 0.67 mmol) and propyl bromide (0.031 mL, 0.35 mmol) were added. Reaction time: 1 hour. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white crystalline solid (0.117 g, 97%). Mp: 40-42 °C; $[\alpha]^{20}_D$ = +81.6° (c = 0.38, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.2 Hz, 1H, ArH), 7.75 (d, *J* = 7.8 Hz, 1H, ArH), 7.66 – 7.59 (m, 1H, ArH), 7.57 – 7.50 (m, 2H, ArH), 7.36 (d, *J* = 8.1 Hz, 1H, ArH), 7.28 – 7.21 (m, 1H, ArH), 7.20 – 7.13 (m, 2H, ArH), 4.65 – 4.55 (m, 1H, H-3), 4.32 (t, *J* = 8.1 Hz, 1H, H-2), 4.20 (dd, *J* = 8.8, 6.5 Hz, 1H, H-2), 4.09 (t, *J* = 7.0 Hz, 2H, *N*-CH_2), 3.46 (dd, *J* = 14.7, 5.3 Hz, 1H, CH_2-indole), 3.20 (dd, *J* = 14.7, 8.9 Hz, 1H, CH_2-indole), 1.89 (dq, *J* = 14.4, 7.2 Hz, 2H, CH_2), 1.71 (s, 3H, CH_3), 0.96 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.45 (C=O), 147.49 (Cq), 136.37 (Cq), 133.26 (ArCH), 131.81 (Cq), 130.20 (ArCH), 128.28 (Cq), 126.40 (ArCH), 124.36 (ArCH), 122.20 (ArCH), 121.66 (ArCH), 119.16 (ArCH), 119.05 (ArCH), 110.09 (Cq), 109.54 (ArCH), 99.04 (C-9b), 74.78 (C-2), 56.31 (C-3), 48.03 (*N*-CH_2), 30.65 (CH_2-indole), 23.68 ($\underline{C}H_2CH_3$), 23.23 (CH_3), 11.65 ($CH_2\underline{C}H_3$). MS (ESI) m/z calcd for $C_{23}H_{24}N_2O_2$: 360.2, found 361 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-acetyl-1*H*-indol-3-yl)methyl)-9b-methyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 5. Following the general procedure for *N*-acetylation, to a stirred solution of (*S*)-tryptophanol-derived oxazoloisoindolinone **1** (0.052 g, 0.16 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0082 g, 0.34 mmol) and acetic anhydride (0.037 mL, 0.36 mmol) were added. Reaction time: 3 hours. Eluent for flash chromatography: 1:1, *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.049 g, 83%). Mp: 65-67 °C; $[\alpha]^{20}_D$ = +25.3° (c = 0.53, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 7.8 Hz, 1H, ArH), 7.73 (s, 1H, ArH), 7.66 (d, *J* = 7.3 Hz,

1H, ArH), 7.51 (t, *J* = 7.8 Hz, 2H, ArH), 7.46 – 7.38 (m, 2H, ArH), 7.29 – 7.22 (m, 1H, ArH), 7.22 – 7.16 (m, 1H, ArH), 4.58 – 4.48 (m, 1H, H-3), 4.30 (dd, *J* = 8.7, 7.6 Hz, 1H, H-2), 4.06 (dd, *J* = 8.8, 5.8 Hz, 1H, H-2), 3.19 (ddd, *J* = 15.7, 7.9, 1.0 Hz, 1H, CH_2-indole), 2.95 (dd, *J* = 15.7, 5.9 Hz, 1H, CH_2-indole), 2.56 (s, 3H, $COCH_3$), 1.64 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.70 (C=O), 168.91 (C=O), 147.33 (Cq), 135.88 (Cq), 133.57 (ArCH), 131.41 (Cq), 130.76 (Cq), 130.40 (ArCH), 125.48 (ArCH), 124.43 (ArCH), 123.68 (ArCH), 123.42 (ArCH), 122.27 (ArCH), 118.74 (ArCH), 118.54 (ArCH), 116.85 (Cq), 99.30 (C-9b), 74.98 (C-2), 55.04 (C-3), 30.72 (CH_2-indole), 24.23 ($CO\underline{C}H_3$), 23.41 (CH_3). Elemental anal. Calc. ($C_{22}H_{20}N_2O_3$): C 73.32%; H 5.59%; N 7.77%. Found C 73.11%, H 5.67%; N 7.71%.

***tert*-butyl 3-(((3*S*,9b*R*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-3-yl)methyl)-1*H*-indole-1-carboxylate 6**. According to the general procedure *N*-Boc protection, in a suspension of compound **1** (0.098 g, 0.31 mmol) in dry tetrahydrofuran (6 mL) dry triethylamine (0.110 mL, 0.79 mmol), 4-dimethylaminopyridine (0.0096 g, 0.079 mmol) and di-tert-butyl bicarbonate (0.086 g, 0.393 mmol) were subsequently added. Reaction time: 3 hours. Eluent for flash chromatography: 2:1 *n*-hexane/ Ethyl acetate. The product was obtained as a light white solid (0.109 g, 84%). Mp: 188-190 °C; $[\alpha]^{20}_D$ = +3.67° (c = 0.10, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.8 Hz, 1H, ArCH), 7.78 (d, *J* = 7.3 Hz 1H, ArCH), 7.70 (d, *J* = 7.2 Hz, 1H, ArCH), 7.63 (s, 1H, ArCH), 7.60 (dd, J = 7.4, 1.2 Hz, 1H, ArH), 7.56 – 7.49 (m, 2H, ArCH), 7.34 (dt, *J* = 7.3, 1.2 Hz, 1H, ArCH), 7.28 (td, *J* = 7.5, 1.2 Hz, 1H), 4.63 – 4.52 (m, 1H, H-3), 4.33 (dd, *J* = 8.9, 7.4 Hz, 1H, H-2), 4.16 (dd, *J* = 9.0, 6.4 Hz, 1H, H-2), 3.37 (ddd, *J* = 14.7, 5.4, 1.0 Hz, 1H, CH_2-indole), 3.10 (dd, *J* = 14.8, 9.0 Hz, 1H, CH_2-indole), 1.74 (s, 3H, CH_3), 1.68 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.48 (C=O), 149.82 (C=O), 147.45 (Cq), 135.57 (Cq), 133.38 (ArCH), 131.66 (Cq), 130.64 (Cq), 130.28 (ArCH), 124.68 (ArCH), 124.45 (ArCH), 123.75 (ArCH), 122.75 (ArCH), 122.26 (ArCH), 119.25 (ArCH), 116.54 (Cq), 115.40 (ArCH), 99.07 (C-9b), 83.76 ($\underline{C}(CH_3)_3$), 74.71 (C-2), 55.52 (C-3), 30.75 (CH_2-indole), 28.34 ($C(\underline{C}H_3)_3$), 23.31 (CH_3). MS (ESI) m/z calcd for $C_{25}H_{26}N_2O_4$: 418.2, found: 419 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-benzoyl-1*H*-indol-3-yl)methyl)-9b-methyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 8. Following the general procedure for *N*-benzoylation, to a stirred solution of (*S*)-tryptophanol-derived oxazoloisoindolinone **1** (0.056 g, 0.18 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0097 g, 0.40 mmol) and benzoyl chloride (0.044 mL, 0.35 mmol) were added. Reaction time: 2 hours. Eluent for flash chromatography: 6:4, *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.057 g, 77%). Mp: 56-58 °C; $[\alpha]^{20}_D$ = +51.8° (c = 0.39, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 7.0, 1.3 Hz, 1H, ArH), 7.78 – 7.70 (m,4H, ArH), 7.66 – 7.49 (m, 6H, ArH), 7.45 – 7.33 (m, 3H, ArH), 4.59 – 4.48 (m, 1H, H-3), 4.31 (dd, *J* = 8.9, 7.4 Hz, 1H, H-2), 4.12 (dd, *J* = 8.9, 6.2 Hz, 1H, H-2), 3.34 (ddd, *J* = 14.9, 6.0, 1.1 Hz, 1H, CH_2-indole), 3.08 (ddd, *J* = 14.9, 8.5, 0.4 Hz, 1H, CH_2-indole), 1.72 (s, 1H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.49 (C=O), 168.63 (C=O), 147.39 (Cq), 136.44 (Cq), 134.69 (Cq), 133.50 (ArCH), 132.05 (ArCH), 131.53 (ArCH), 131.01 (ArCH), 130.71 (Cq), 130.37 (ArCH), 129.36 (ArCH), 129.02 (Cq), 128.78 (ArCH), 125.47 (ArCH), 125.38 (ArCH), 124.47 (ArCH), 124.11 (ArCH), 122.29 (ArCH), 119.18 (ArCH), 117.98 (Cq), 116.72 (ArCH), 99.11 (C-9b), 74.67 (C-2), 55.46 (C-3), 30.65 (CH_2-indole), 23.38 (CH_3). MS (ESI) m/z calcd for $C_{27}H_{22}N_2O_3$: 422.16, found 423.15 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-tosyl-1*H*-indol-3-yl)methyl)-9b-methyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 9. Following the general procedure for *N*-tosylation, to a stirred solution of (*S*)-tryptophanol-derived oxazoloisoindolinone **1** (0.10 g, 0.26 mmol) in 3 mL of dimethylformamide, sodium hydride (0.0013 g, 0.54 mmol) and *p*-toluenesulfonyl chloride (0.050 g, 0.26 mmol) were added. Reaction time: 3 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.097 g, 78%). Mp: 220-222 °C; $[\alpha]^{20}_D$ = +60.7° (c = 0.10, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 1H, ArH), 7.77 (dd, *J* = 8.5, 1.9 Hz, 3H, ArH), 7.65 – 7.59 (m, 2H, ArH), 7.60 (s, 1H, ArH), 7.53 (t, *J* = 7.0 Hz, 2H, ArH), 7.33 (dt, J = 7.24, 0.8 Hz, 1H, ArH), 7.26 (dt, J = 7.7, 0.8 Hz, 1H, ArH), 7.20 (d, *J* = 8.1 Hz, 2H, ArH), 4.55 – 4.47 (m, 1H, H-3), 4.31 (dd, *J* = 8.8, 7.6 Hz, 1H, H-2), 4.10 (dd, *J* = 8.9, 6.5 Hz, 1H, H-2), 3.28 (dd, *J* = 14.9, 5.0 Hz, 1H, CH_2-indole), 3.09 (dd, *J* = 14.9, 8.3 Hz, 1H, CH_2-indole), 2.32 (s, 3H, $ArCH_3$), 1.61 (s, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.50 (C=O), 147.32 (Cq), 144.98 (Cq), 135.31 (Cq), 133.48 (ArCH), 131.54 (Cq), 131.02 (Cq), 130.37 (ArCH**),** 129.95 (ArCH), 126.95 (ArCH), 125.05 (ArCH), 124.47 (ArCH), 124.18 (ArCH), 123.43 (ArCH), 122.28 (ArCH), 119.74 (ArCH), 118.66 (Cq), 113.90 (ArCH), 99.10 (C-9b), 74.50 (C-2), 55.21 (C-3), 30.46 (CH_2-indole), 23.08 ($ArCH_3$), 21.69 (CH_3). MS (ESI) m/z calcd for $C_{27}H_{24}N_2O_4S$: 472.2, found 473.3 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 10. Following the general procedure for cyclocondensation reactions, (*S*)-tryptophanol (0.20

g, 1.06 mmol) and 2-benzoylbenzoic acid (0.29 g, 1.26 mmol) were dissolved in 10 mL of toluene. Reaction time: 19 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane 4:6. The compound was obtained as an off-white powder. Yield: 0.33 g, 81%. [26]. Mp: 227-229°C; $[\alpha]^{20}_D$ = +82.0° (c = 0.18, CH_2Cl_2). ^{13}C NMR (101 MHz, DMSO) δ 173.90 (C=O), 147.34 (Cq), 139.23 (Cq), 136.54 (Cq), 136.38 (Cq), 134.16 (ArCH), 130.92 (ArCH), 130.83 (ArCH), 129.30 (2xArCH), 129.19 (ArCH), 127.52 (Cq), 126.00 (2xArCH), 124.36 (ArCH), 124.05 (ArCH), 123.42 (ArCH), 123.26 (ArCH), 121.48 (ArCH), 118.84 (ArCH), 118.30 (ArCH), 111.88 (ArCH), 110.36 (Cq), 100.79 (C-9b), 76.24 (C-2), 55.87 (C-3), 30.31 (CH_2-Indole) ppm; MS (ESI) m/z calcd for $C_{27}H_{24}N_2O_2$: 380.2, found 381 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-methyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 11. Following the general procedure for *N*-methylation, to a stirred solution of compound **10** (0.10g, 0.27 mmol) in 2 mL of dimethylformamide, sodium hydride (0.014g, 0,60 mmol) and methyl iodide (0.025 mL, 0.41 mmol) were added. Reaction time: one hour. Eluent for flash chromatography: ethyl acetate/ *n*-hexane 1:1. The product was obtained as a white crystalline solid (0.096g, 89%). Mp: 148-150°C; $[\alpha]^{20}_D$ = +84.5° (c = 0.37, CH_2Cl_2), as described in literature [25].

(3*S*,9b*R*)-3-((1-ethyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 12. Following the general procedure for *N*-ethylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.053 g, 0.14 mmol) in 2 mL of dimethylformamide, sodium hydride (0.007 g, 0.28 mmol) and ethyl iodide (0.022 mL, 0.28 mmol) were added. Reaction time: 30 minutes. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.040 g, 71%). Mp: 58-60 °C; $[\alpha]^{20}_D$ = +76.9° (c = 0.39, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.78 (m, 1H, ArH), 7.68 – 7.61 (m, 2H, ArH), 7.53 – 7.45 (m, 3H, ArH), 7.43 – 7.37 (m, 3H, ArH), 7.30 (d, *J* = 8.2 Hz, 1H, ArH), 7.25 – 7.22 (m, 1H, ArH), 7.19 (d, *J* = 8.1 Hz, 1H, ArH), 7.08 (t, *J* = 7.5 Hz, 1H, ArH), 7.04 (s, 1H, ArH), 4.70 (m, 1H, H-3), 4.45 (t, *J* = 8.1 Hz, 1H, H-2), 4.10 (q, *J* = 7.2 Hz, 2H, *N*-CH_2), 3.99 (dd, *J* = 8.2, 7.2 Hz, 1H, H-2), 3.23 (dd, *J* = 14.6, 5.8 Hz, 1H, CH_2-indole), 2.65 (dd, *J* = 14.6, 9.4 Hz, 1H, CH_2-indole), 1.42 (t, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.71 (C=O), 147.28 (Cq), 138.99 (Cq), 136.02 (Cq), 133.38 (ArCH), 131.23 (Cq), 130.21 (ArCH), 128.89 (ArCH), 128.79 (ArCH), 128.12 (Cq), 125.93 (ArCH), 125.22 (ArCH), 124.49 (ArCH), 123.57 (ArCH), 121.62 (ArCH), 119.12 (ArCH), 118.97 (ArCH), 110.38 (Cq), 109.34 (ArCH), 101.06 (C-9b), 76.47 (C-2), 55.90 (C-3), 40.91 (*N*-CH_2), 30.26 (CH_2-indole), 15.60 (CH_3). MS (ESI) m/z calcd for $C_{27}H_{24}N_2O_2$: 408, found 409 $[M+H]^+$.

(3*S*,9b*R*)-9b-phenyl-3-((1-propyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 13. Following the general procedure for *N*-propylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.059 g, 0.16 mmol) in 2 mL of dimethylformamide, sodium hydride (0.008 g, 0.31 mmol) and propyl bromide (0.028 mL, 0.31 mmol) were added. Reaction time: 1 hour. Eluent for flash chromatography: 6:4, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white crystalline solid (0.051 g, 77%). Mp: 52-54 °C; $[\alpha]^{20}_D$ = +71.8° (c = 0.39, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 1H, ArH), 7.67 – 7.61 (m, 3 H, ArH), 7.51 – 7.45 (m, 3H, ArH), 7.42 – 7.37 (m, 2H, ArH), 7.28 (d, *J* = 8.3 Hz, 1H, ArH), 7.25 – 7.21 (m, 1H, ArH), 7.21 – 7.15 (m, 1H, ArH), 7.10 – 7.03 (m, 1H, ArH), 7.01 (s, 1H, ArH), 4.69 (m, 1H, H-3), 4.43 (dd, *J* = 8.7, 7.5 Hz, 1H, H-2), 3.99 (m, 3H, *N*-CH_2 and H-2), 3.23 (ddd, *J* = 14.6, 5.8, 0.7 Hz, 1H, CH_2-indole), 2.63 (dd, *J* = 14.7, 9.5 Hz, 1H, CH_2-indole), 1.83 (sextet, *J* = 7.26 Hz, 2H, $C\underline{H_2}CH_3$), 0.90 (t, *J* = 7.4 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.71 (C=O), 147.31 (Cq), 139.04 (Cq), 136.34 (Cq), 133.38 (ArCH), 131.25 (Cq), 130.21 (ArCH), 128.90 (ArCH), 128.80 (ArCH), 128.08 (Cq), 126.08 (ArCH), 125.94 (ArCH), 124.50 (ArCH), 123.58 (ArCH), 121.60 (ArCH), 119.09 (ArCH), 118.93 (ArCH), 110.17 (Cq), 109.49 (ArCH), 101.07 (C-9b), 76.45 (C-2), 55.91 (C-3), 48.03 (*N*-CH_2), 30.25 (CH_2-indole), 23.64 ($\underline{C}H_2CH_3$), 11.68 (CH_3). MS (ESI) m/z calcd for $C_{28}H_{26}N_2O_2$: 422.2, found 423.2 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-acetyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 14. Following the general procedure for *N*-acetylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.052 g, 0.14 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0066 g, 0.27 mmol) and acetic anhydride (0.026 mL, 0.27 mmol) were added. Reaction time: 3 hours. Eluent for flash chromatography: 1:1, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.047 g, 81%). Mp: 126-127 °C; $[\alpha]^{20}_D$ = +77.5° (c = 0.40, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, *J* = 8.4 Hz, 1H, ArH), 7.84 – 7.78 (m, 1H, ArH), 7.75 (s, 1H, ArH), 7.58 – 7.45 (m, 4H, ArH), 7.41 – 7.30 (m, 5H, ArH), 7.29 – 7.20 (m, 2H, ArH), 4.83 – 4.71 (m, 1H, H-3), 4.63 (t, *J* = 8.0 Hz, 1H, H-2), 4.02 (dd, *J* = 8.3, 6.7 Hz, 1H, H-2), 2.90 (dd, *J* = 15.6, 8.1 Hz, 1H, CH_2-indole), 2.71 (d, *J* = 6.5 Hz, 1H, CH_2-indole), 2.66 (s, 3H, $COCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.92 (C=O),

168.89 (C=O), 147.10 (Cq), 138.55 (Cq), 135.89 (Cq), 133.60 (ArCH), 130.87 (Cq), 130.73 (Cq), 130.36 (ArCH), 128.95 (2xArCH), 128.92 (ArCH), 125.78 (2xArCH), 125.39 (ArCH), 124.53 (ArCH), 123.62 (ArCH), 123.58 (ArCH), 123.31 (ArCH), 118.71 (ArCH), 118.56 (Cq), 116.78 (ArCH), 101.31 (C-9b), 76.35 (C-2), 54.62 (C-3), 29.79 (CH_2-indole), 24.25 (CH_3). Elemental anal. Calc. ($C_{27}H_{22}N_2O_3$): C 76.76%; H 5.25%; N 6.63%. Found C 76.91%, H 5.31%; N 6.69%.

***tert*-butyl 3-(((3S,9bR)-5-oxo-9b-phenyl-2,3,5,9b-tetrahydrooxazolo[2,3-*a*]isoindol-3-yl)methyl)-1*H*-indole-1-carboxylate 15**. Following the general procedure for *N*-Boc protection, to a solution of tryptophanol-derived oxazoloisoindolinone **10** (0.050 g, 0.131 mmol) in dry tetrahydrofuran (6 mL) was added dry triethylamine (0.040 mL, 0.289 mmol, d = 0.728 g/mL), 4-dimethylaminopyridine (0.004 g, 0.32 mmol) and di-*tert*-butyl bicarbonate (0.0372 g, 0.170 mmol) was added to the reaction mixture, at room temperature. Reaction time: 3 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 4:6. The product was obtained as a white light solid (0.054g, 86%). Mp: 51-53 °C; $[\alpha]^{20}_D$ = +91.9° (c = 0.10, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (d, J = 7.8 Hz, 1H, ArH), 7.82 – 7.76 (m, 1H, ArH), 7.62 – 7.56 (m, 2H, ArH), 7.52 – 7.46 (m, 2H, ArH), 7.44 (s, 1H, ArH), 7.40 – 7.35 (m, 3H, ArH), 7.31 (td, J = 7.4, 1.1 Hz, 1H, ArH), 7.25 – 7.18 (m, 2H, ArH), 4.69 (dq, J = 8.8, 6.9 Hz, 1H, H-3), 4.49 (dd, J = 8.6, 7.6 Hz, 1H, H-2), 3.98 (dd, J = 8.7, 6.8 Hz, 1H, H-2), 3.10 (dd, J = 14.8, 5.8 Hz, 1H, CH_2-indole), 2.63 (dd, J = 14.8, 9.0 Hz, 1H, CH_2-indole), 1.66 (s, 9H, $C(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.79 (C=O), 149.81 (C=O), 147.33 (Cq), 138.88 (Cq), 135.52 (Cq), 133.48 (ArCH), 131.09 (Cq), 130.57 (Cq), 130.27 (ArCH), 128.91 (ArCH), 128.82 (ArCH), 125.88 (ArCH), 124.58 (ArCH), 124.51 (ArCH), 123.62 (ArCH), 123.54 (ArCH), 122.67 (ArCH), 119.12 (ArCH), 116.46 (Cq), 115.36 (ArCH), 101.12 (C-9b), 83.70 ($\underline{C}(CH_3)_3$), 76.19 (C-2), 55.23 (C-3), 29.96 (CH_2-indole), 28.38 ($C(\underline{C}H_3)_3$). MS (ESI) m/z calcd for $C_{30}H_{28}N_2O_4$: 480.2, found 481 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-benzyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 16. Following the general procedure of N-benzylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.064 g, 0.17 mmol) in 2 mL dimethylformamide, sodium hydride (0.0089 g, 0.37 mmol) and benzyl bromide (0.030 mL, 0.25 mmol) were added. Reaction time: 2 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.076 g, 96%). Mp: 61-63 °C; $[\alpha]^{20}_D$ = +62.7° (c = 0.42, CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 1H, ArH), 7.67 – 7.60 (m, 2H, ArH), 7.53 (d, *J* = 7.6 Hz, 1H, ArH), 7.48 (dd, *J* = 5.6, 3.1 Hz, 2H, ArH), 7.42 – 7.35 (m, 4H, ArH), 7.32 – 7.27 (m, 1H, ArH), 7.25 – 7.20 (m, 3H, ArH), 7.17 (dd, *J* = 6.9, 1.0 Hz, 1H, ArH), 7.13 (dd, *J* = 5.6, 1.3 Hz, 1H, ArH), 7.08 (d, *J* = 7.6 Hz, 2H, ArH), 7.01 (s, 1H, ArH), 5.25 (s, 2H, *N*-CH_2), 4.74-4.67 (m, 1H, H-3), 4.44 (dd, *J* = 8.6, 7.5 Hz, 1H, H-2), 3.99 (dd, *J* = 8.7, 6.7 Hz, 1H, H-2), 3.23 (dd, *J* = 14.5, 5.9 Hz, 1H, CH_2-indole), 2.66 (dd, *J* = 14.6, 9.5 Hz, 1H, CH_2-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.68 (C=O), 147.31 (Cq), 139.02 (Cq), 137.72 (Cq), 136.69 (Cq), 133.39 (ArCH), 131.22 (Cq), 130.21 (Cq), 128.90 (2xArCH), 128.87 (2xArCH), 128.80 (ArCH), 128.25 (Cq), 127.69 (ArCH), 126.88 (2xArCH), 126.39 (ArCH), 125.93 (2xArCH), 124.50 (ArCH), 123.58 (ArCH), 122.02 (ArCH), 119.34 (ArCH), 119.17 (ArCH), 111.10 (ArCH), 109.79 (ArCH), 101.06 (C-9b), 76.40 (C-2), 55.87 (C-3), 50.06 (*N*-CH_2), 30.27 (CH_2-indole). MS (ESI) m/z calcd for $C_{32}H_{26}N_2O_3$: 470.2, found 471.3 $[M+H]^+$.

(3*S*,9b*R*)-3-((1-benzoyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 17. Following the general procedure for *N*-benzoylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.061 g, 0.16 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0078 g, 0.32 mmol) and benzoyl chloride (0.037 mL, 0.32 mmol) were added. Reaction time: 2.5 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.053 g, 68%). Mp: 70-72 °C; $[\alpha]^{20}_D$ = + 46.2° (c = 0.26, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.0 Hz, 1H, ArH), 7.82 – 7.74 (m, 1H, ArH), 7.71 (d, *J* = 7.7 Hz, 2H, ArH), 7.65 – 7.59 (m, 1H, ArH), 7.58 – 7.44 (m, 7H, ArH), 7.39 (td, J = 7.0 1.1 Hz, 1H, ArH), 7.36 – 7.28 (m, 4H, ArH), 7.23 – 7.20 (m, 1H, ArH), 7.19 (s, 1H, ArH), 4.71 – 4.60 (m, 1H, H-3), 4.51 (dd, *J* = 8.5, 8.5 Hz, 1H, H-2), 3.95 (dd, *J* = 8.5, 6.7 Hz, 1H, H-2), 3.02 (dd, *J* = 15.0, 6.4 Hz, 1H, CH_2-indole), 2.67 (dd, *J* = 14.9, 8.2 Hz, 1H, CH_2-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.77 (C=O), 168.54 (C=O), 147.25 (Cq), 138.76 (Cq), 136.35 (Cq), 134.70 (Cq), 133.55 (ArCH), 131.97 (ArCH), 130.96 (Cq), 130.90 (Cq), 130.30 (ArCH), 129.36 (ArCH), 128.91 (ArCH), 128.86 (ArCH), 128.72 (ArCH), 125.77 (ArCH), 125.34 (ArCH), 125.23 (ArCH), 124.51 (ArCH), 124.00 (ArCH), 123.62 (ArCH), 119.07 (ArCH), 117.88 (Cq), 116.65 (ArCH), 101.11 (C-9b), 76.05 (C-2), 55.19 (C-3), 29.68 (CH_2-indole). MS (ESI) m/z calcd for $C_{32}H_{24}N_2O_3$: 484.18, found 485.21 $[M+H]^+$.

(3*S*,9b*R*)-9b-phenyl-3-((1-tosyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 18. Following the general procedure for *N*-tosylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **10** (0.099 g, 0.26 mmol) in 3 mL of dimethylformamide,

sodium hydride (0.0014 g, 0.60 mmol) and *p*-toluenesulfonyl chloride (0.10 g, 0.55 mmol) were added. Reaction time: 3 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.13 g, 96%). Mp: 218-220 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.1 Hz, 1H, ArH), 7.81 (dd, *J* = 5.6, 3.1 Hz, 1H, ArH), 7.74 (d, *J* = 8.3 Hz, 2H, ArH), 7.55 (dd, *J* = 6.6, 3.0 Hz, 2H, ArH), 7.52 – 7.45 (m, 3H, ArH), 7.41 (d, *J* = 7.7 Hz, 1H, ArH), 7.38 – 7.34 (m, 3H, ArH), 7.34 – 7.27 (m, 1H, ArH), 7.25 – 7.21 (m, 2H, ArH), 7.18 (d, *J* = 8.2 Hz, 2H, ArH), 4.71 – 4.60 (m, 1H, H-3), 4.46 (dd, *J* = 8.0, 8.0 Hz, 1H, H-2), 3.93 (dd, *J* = 8.6, 6.5 Hz, 1H, H-2), 3.01 (dd, *J* = 14.9, 6.7 Hz, 1H, CH_2-indole), 2.58 (dd, *J* = 15.0, 8.5 Hz, 1H, CH_2-indole), 2.29 (s, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.63 (C=O), 147.19 (Cq), 144.90 (Cq), 138.67 (Cq), 135.32 (Cq), 135.29 (ArCH), 133.56 (ArCH), 130.91 (Cq), 130.83 (Cq), 130.32 (ArCH), 129.90 (2xArCH), 128.96 (2xArCH), 128.94 (ArCH), 126.92 (2xArCH), 125.76 (2xArCH), 124.96 (ArCH), 124.51 (ArCH), 123.91 (ArCH), 123.63 (Cq), 123.33 (ArCH), 119.50 (ArCH), 118.76 (Cq), 113.91 (ArCH), 101.07 (C-9b), 76.12 (C-2), 54.73 (C-3), 30.00 (CH_2-indole), 21.67 (CH_3). MS (ESI) m/z calcd for $C_{32}H_{26}N_2O_4S$: 534.16, found 535.23 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-fluorophenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 19. Following the general procedure for cyclocondensation reactions, to a solution of (*S*)-tryptophanol (0.172 g, 0.905 mmol) in toluene (7.5 mL) was added 2-(4-fluorobenzoyl)benzoic acid (0.412 g, 1.09 mmol). Reaction time: 23 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 1:1. The product was obtained as a white solid (0.207 g, 65.9%). Mp: 204-206 °C; $[\alpha]^{20}_D$ = +147.4° (c = 0.15 CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (s, 1H, N*H*), 7.83 – 7.76 (m, 1H, Ar*H*), 7.62 – 7.54 (m, 2H, Ar*H*), 7.54 – 7.45 (m, 3H, Ar*H*), 7.34 (d, *J* = 7.7 Hz, 1H, Ar*H*), 7.22 – 7.01 (m, 6H, Ar*H*), 4.72 (m, 1H, *H*-3), 4.47 (dd, *J* = 8.7, 7.5 Hz, 1H, *H*-2), 3.98 (dd, *J* = 8.8, 6.7 Hz, 1H, *H*-2), 3.17 (ddd, *J* = 14.8, 6.3, 0.9 Hz, 1H, C*H*$_2$-indole), 2.68 (dd, *J* = 14.7, 9.0 Hz, 1H, C*H*$_2$-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.47 (*C*=O), 163.08 (d, *J* = 245.9 Hz, Cq), 147.19 (Cq), 136.26 (Cq), 134.89 (Cq), 133.52 (ArCH), 131.06 (Cq), 130.34 (ArCH), 127.82 (d, *J* = 8.3 Hz, ArCH), 127.58 (Cq), 124.56 (ArCH), 123.47 (ArCH), 122.30 (ArCH), 122.24 (ArCH), 119.64 (ArCH), 118.85 (ArCH), 115.85 (d, *J* = 21.6 Hz, ArCH), 111.84 (Cq), 111.24 (ArCH), 100.77 (*C*-9b), 76.40 (*C*-2), 55.88 (*C*-3), 30.20 (CH_2-indole). MS (ESI) m/z calcd for $C_{25}H_{19}FN_2O_2$: 398.4, found 399 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-chlorophenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 20. Following the general procedure for cyclocondensation reactions, to a solution of (*S*)-tryptophanol (0.113g, 0.593 mmol) in 5 mL toluene 2-(4-chlorobenzoyl)benzoic acid (0.185g, 0.711 mmol) was added. Reaction time: 16 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane 1:1. The compound was obtained as a white crystalline powder. Yield: 0.209 g, 84.9%. Mp: 88-90 °C; $[\alpha]^{20}_D$ = +161.7° (c = 0.13, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H, NH), 7.84 – 7.77 (m, 1H, ArH), 7.56 – 7.48 (m, 5H, ArH), 7.38 – 7.33 (m, 3H, ArH), 7.23 – 7.16 (m, 2H, ArH), 7.16 – 7.09 (m, 2H, ArH), 4.72 (m, 1H, H-3), 4.47 (dd, J = 8.7, 7.5 Hz, 1H, H-2), 3.98 (dd, J = 8.8, 6.7 Hz, 1H, H-2), 3.22 –3.10 (dd, J = 14.8, 5.7 Hz, 1H, CH_2-indole),2.70 (dd, J = 14.8, 8.8 Hz, 1H, CH_2-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.70 (C=O), 146.92 (Cq), 137.67 (Cq), 136.23 (Cq), 134.71 (Cq), 133.55 (ArCH), 131.01 (Cq), 130.41 (ArCH), 129.08 (ArCH), 127.49 (ArCH), 127.35 (Cq), 124.54 (ArCH), 123.46 (ArCH), 122.31 (ArCH), 122.21 (ArCH), 119.55 (ArCH), 118.79 (ArCH), 111.57 (Cq), 111.27 (ArCH), 100.66 (C-9b), 76.36 (C-2), 55.91 (C-3), 30.15 (CH_2-indole). MS (ESI) m/z calcd for $C_{25}H_{18}ClN_2O_2$: 414.1, found 415 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-chloro-3-nitrophenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 21. Following the general procedure for cyclocondensation reactions, to a solution of (*S*)-tryptophanol (0.152 g, 0.803 mmol) in toluene (7.5 mL) was added 2-(4-chloro-3-nitrophenyl)benzoic acid (0.233 g, 0.762 mmol). Reaction time: 16.5 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 4:6. The product was obtained as a yellow light solid (0.141 g, 44.5%). Mp: 94-96 °C; $[\alpha]^{20}_D$ = +55.8° (c = 0.43, CH_2Cl_2). The ^{1}H NMR spectrum was found identical to the one of compound **32**. MS (ESI) m/z calcd for $C_{25}H_{19}ClN_3O_4$: 459.09, found 460 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-methoxyphenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 22. Following the general procedure for cyclocondensation reactions, to a solution of (*S*)-tryptophanol (0.0365 g, 0.192 mmol) in toluene (2 mL) was added 2-(4-methoxybenzoyl)benzoic acid (0.0478 g, 0.187 mmol). Reaction time: 16 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 1:1. The product was obtained as a white solid (0.0423 g, 55.3%). Mp: 77-79 °C; $[\alpha]^{20}_D$ = +153.3° (c = 0.079, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H, NH), 7.78 (dt, *J* = 6.7, 2.8 Hz, 1H, ArH), 7.58 – 7.50 (m, 3H, ArH), 7.50 – 7.44 (m, 2H, ArH), 7.35 (d, *J* = 8.1 Hz, 1H, ArH), 7.25 – 7.20 (m, 1H, ArH), 7.18 (td, *J* = 5.6, 2.0 Hz, 2H, ArH),

7.14 – 7.07 (m, 1H, ArH), 6.94 – 6.87 (m, 2H, ArH), 4.70 (td, *J* = 13.9, 6.6 Hz, 1H, H-3), 4.47 (dd, *J* = 8.7, 7.5 Hz, 1H, H-2), 3.99 (dd, *J* = 8.7, 6.7 Hz, 1H, H-2), 3.83 (s, 3H, OCH_3), 3.20 (dd, *J* = 14.7, 6.4 Hz, 1H, CH_2-indole), 2.69 (dd, *J* = 14.6, 8.9 Hz, 1H, CH_2-indole); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.76 (*C*=O), 160.00 (Cq), 147.47 (Cq), 136.23 (Cq), 133.41 (ArCH), 131.08 (ArCH), 130.76 (ArCH), 130.12 (ArCH), 127.56 (ArCH), 127.24 (Cq), 124.43 (ArCH), 123.45 (ArCH), 122.26 (ArCH), 122.21 (ArCH), 119.53 (ArCH), 118.91 (ArCH), 114.23 (ArCH), 112.00 (ArCH), 111.22 (Cq), 101.02 (C-9b), 76.46 (C-2), 55.70 (C-3), 55.44 (OCH_3), 30.28 (CH_2-indole). MS (ESI) m/z calcd for $C_{26}H_{22}N_2O_3$: 410.5, found 411 $[M+H]^+$.

(3*S*,9b*R*)-3-((1*H*-indol-3-yl)methyl)-9b-(*p*-tolyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 23. Following the general procedure for cyclocondensation reactions, to a solution of (*S*)-tryptophanol (0.177 g, 0.931 mmol) in toluene (7.5 mL) was added 2-(4-methylbenzoyl)benzoic acid (0.262 g, 1.12 mmol). Reaction time: 17 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 6:4. The product was obtained as a white solid (0.302 g, 82.2%). Mp: 155-157 °C; $[\alpha]^{20}_D$ = +169.8° (c = 0.10, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (s, 1H, NH), 7.81 – 7.77 (m, 1H, ArH), 7.52 (d, *J* = 8.1 Hz, 3H, ArH), 7.49 – 7.45 (m, 2H, ArH), 7.34 (d, *J* = 8.0 Hz, 1H, ArH), 7.25 – 7.16 (m, 1H, ArH), 7.20 (d, *J* = 7.8 Hz, 3H, Ar*H*), 7.15 (s, 1H, ArH), 7.10 (td, *J* = 8.0, 1.0 Hz, 1H, Ar*H*), 4.70 (dq, *J* = 8.8, 6.6 Hz, 1H, H-3), 4.46 (dd, *J* = 8.7, 7.5 Hz, 1H, H-2), 3.99 (dd, *J* = 8.7, 6.7 Hz, 1H, *H*-2), 3.20 (dd, *J* = 14.7, 6.3 Hz, 1H, CH_2-indole), 2.67 (dd, *J* = 14.7, 8.9 Hz, 1H, CH_2-indole), 2.38 (s, 3H, ArCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.62 (*C*=O), 147.29 (Cq), 138.45 (Cq), 136.12 (Cq), 135.78 (Cq), 133.27 (ArCH), 131.05 (ArCH), 130.02 (ArCH), 129.50 (ArCH), 127.45 (Cq), 125.73 (ArCH), 124.32 (ArCH), 123.38 (ArCH), 122.09 (ArCH), 119.43 (ArCH), 118.82 (ArCH), 111.99 (Cq), 111.08 (ArCH), 101.01 (C9b), 76.36 (C-2), 55.62 (C-3), 30.20 (*C*H_2-indole), 21.24 (Ar*C*H_3). MS (ESI) m/z calcd for $C_{26}H_{22}N_2O_2$: 394.2, found 395 $[M+H]^+$.

(3*R*,9b*S*)-3-((1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 24. Following the general procedure for cyclocondensation reactions, (*R*)-tryptophanol (0.20 g, 1.04 mmol) and 2-benzoylbenzoic acid (0.29 g, 1.27 mmol) were dissolved in 10 mL of toluene. Reaction time: 19 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane 1:1. Yield: 0.32 g, 79%. The product was obtained as a white crystalline powder. The ^1H-NMR was found identical to the one of compound **10**.[26] $[\alpha]^{20}_D$ = -79.5° (c = 0. 19, CH_2Cl_2).

(3*R*,9b*S*)-3-((1-methyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 25. Following the general procedure *N*-methylation, starting from tryptophanol-derived oxazoloisoindolinone **24** (0.060 g, 0.16 mmol), DMF (2 mL), sodium hydride (0.008 g, 0.32 mmol) and methyl iodide (0.022 mL, 0.35 mmol). Reaction time: 2 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white crystalline solid (0.059 g, 87%). Mp: 148-150 °C; $[\alpha]^{20}_D$ = -81.9° (c = 0.35, CH_2Cl_2). The ^1H NMR spectrum was identical to the one reported for compound **11**[32]: ^1H NMR (300 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 1H, ArH), 7.67 – 7.59 (m, 2H, ArH), 7.53 – 7.45 (m, 3H, ArH), 7.42 – 7.35 (m, 3H, ArH), 7.28 – 7.17 (m, 3H, ArH), 7.09 (td, *J* = 7.9, 1.0 Hz, 1H, ArH), 6.96 (s, 1H, ArH), 4.69 (m, 1H, H-3), 4.45 (dd, *J* = 8.7, 7.5 Hz, 1H, H-2), 3.99 (dd, *J* = 8.7, 6.7 Hz, 1H, H-2), 3.72 (s, 3H, *N*-CH_3), 3.21 (ddd, *J* = 14.6, 5.9, 0.7 Hz, 1H, CH_2-indole), 2.65 (dd, *J* = 14.7, 9.3 Hz, 1H, CH_2-indole). MS (ESI) m/z calcd for $C_{26}H_{22}N_2O_2$: 394.2, found 395.3 $[M + H]^+$.

(3*R*,9b*S*)-3-((1-ethyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 26. Following the general procedure *N*-ethylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **24** (0.040 g, 0.10 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0049 g, 0.20 mmol) and ethyl iodide (0.016 mL, 0.19 mmol) were added. Reaction time: 30 minutes. Eluent for flash chromatography: 8:2, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.031 g, 72%). Mp: 58-60 °C; $[\alpha]^{20}_D$ = -71.8° (c = 0.39, CH_2Cl_2); The ^1H-NMR spectrum was found identical to the one of compound **12**. MS (ESI) m/z calcd for $C_{27}H_{24}N_2O_2$: 408.2, found 409.3 $[M + H]^+$.

(3*R*,9b*S*)-9b-phenyl-3-((1-propyl-1*H*-indol-3-yl)methyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 27. Following the general procedure *N*-propylation, starting from tryptophanol-derived oxazoloisoindolinone **24** (0.051 g, 0.13 mmol), DMF (2 mL), sodium hydride (0.063 g, 0.26 mmol) and propyl bromide (0.024 mL, 0.28 mmol). Reaction time: 1 hour. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization: *n*-hexane/ethyl acetate. The product was obtained as white crystalline solid (0.051 g, 91%); Mp: 52-54 °C; $[\alpha]^{20}_D$ = -69.2° (c = 0.39, CH_2Cl_2). The ^1H-NMR spectrum was found identical to the one of compound **13**. MS (ESI) m/z calcd for $C_{28}H_{26}N_2O_2$: 422.2, found 423.2 $[M + H]^+$.

(3*R*,9b*S*)-3-((1-acetyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 28. Following the general procedure for *N*-acetylation, to a stirred solution of

tryptophanol-derived oxazoloisoindolinone **24** (0.041 g, 0.11 mmol), sodium hydride (0.0067 g, 0.28 mmol) and acetic anhydride (0.024 mL, 0.25 mmol) were added. Reaction time: 3 hours. Eluent for flash chromatography: 7:3, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.035 g, 77%). Mp: 122-123°C; $[\alpha]^{20}_D$ = -72.5° (c = 0.40, CH_2Cl_2). The ^{1}H-NMR spectrum was found identical to the one of compound **14**. MS (ESI) m/z calcd for $C_{27}H_{22}N_2O_3$: calculated 422.3, found 423.3 $[M+H]^+$.

(3*R*,9b*S*)-3-((1-benzoyl-1*H*-indol-3-yl)methyl)-9b-phenyl-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(*9b*H)-one 29. Following the general procedure for *N*-benzoylation, to a stirred solution of tryptophanol-derived oxazoloisoindolinone **24** (0.037 g, 0.098 mmol) in 2 mL of dimethylformamide, sodium hydride (0.0052 g, 0.22 mmol) and benzoyl chloride (0.023 mL, 0.20 mmol) were added. Reaction time: 2 hours. Eluent for flash chromatography: 6:4, *n*-hexane/ethyl acetate. Recrystallization in *n*-hexane/ethyl acetate. The product was obtained as white light solid (0.039 g, 82%). Mp: 55-57; $[\alpha]^{20}_D$ = -42.3° (c = 0.26, CH_2Cl_2). The ^{1}H-NMR spectrum was found identical to the one of compound **15**. MS (ESI) m/z calcd for $C_{32}H_{24}N_2O_3$: 484.18, found 485.20 $[M+H]^+$.

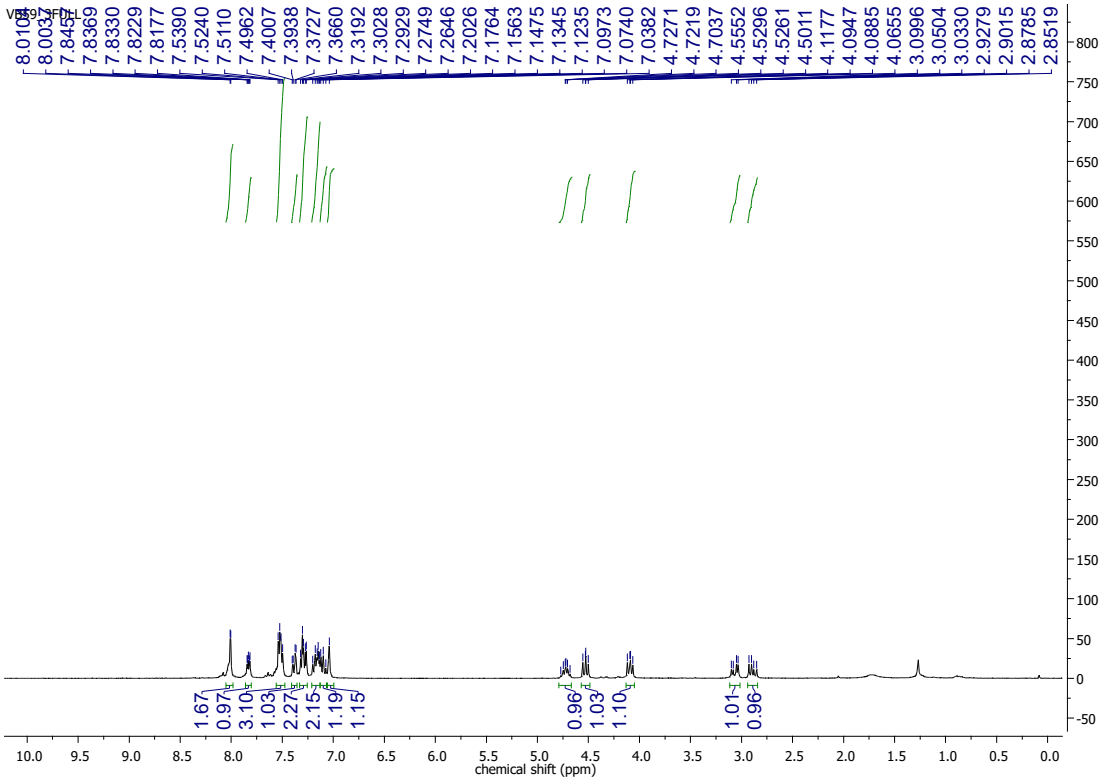
(3*R*,9b*S*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-fluorophenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 30. Following the general procedure for cyclocondensation reactions, to a solution of (*R*)-tryptophanol (0.108 g, 0.569 mmol) in toluene (5 mL) was added 2-(4-fluorobenzoyl)benzoic acid (0.153 g, 0.627 mmol). Reaction time: 16.5 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 4:6. The product was obtained as a white solid (0.133 g, 56%). Mp: 203-207 °C; $[\alpha]^{20}_D$ = -140.3° (c = 0.15, CH_2Cl_2). The ^{1}H NMR spectrum was found identical to the one of compound **19**. MS (ESI) m/z calcd for $C_{25}H_{19}FN_2O_2$: 398.4, found 399 $[M+H]^+$.

(3*R*,9b*S*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-chlorophenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 31. Following the general procedure for cyclocondensation reactions, to a solution of (*R*)-tryptophanol (0.0952 g, 0.500 mmol) in toluene (5 mL) was added 2-(4-chlorobenzoyl)benzoic acid (0.177 g, 0.681 mmol). Reaction time: 15.5 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 1:1. The product was obtained as a white crystalline solid (0.1452 g, 70%). Mp: 84-86 °C; $[\alpha]^{20}_D$ = -138.3° (c = 0.11, CH_2Cl_2). The ^{1}H NMR of the compound was found equal to its enantiomer, compound **20**. MS (ESI) m/z calcd for $C_{25}H_{18}ClN_2O_2$: 414.1, found 415 $[M+H]^+$.

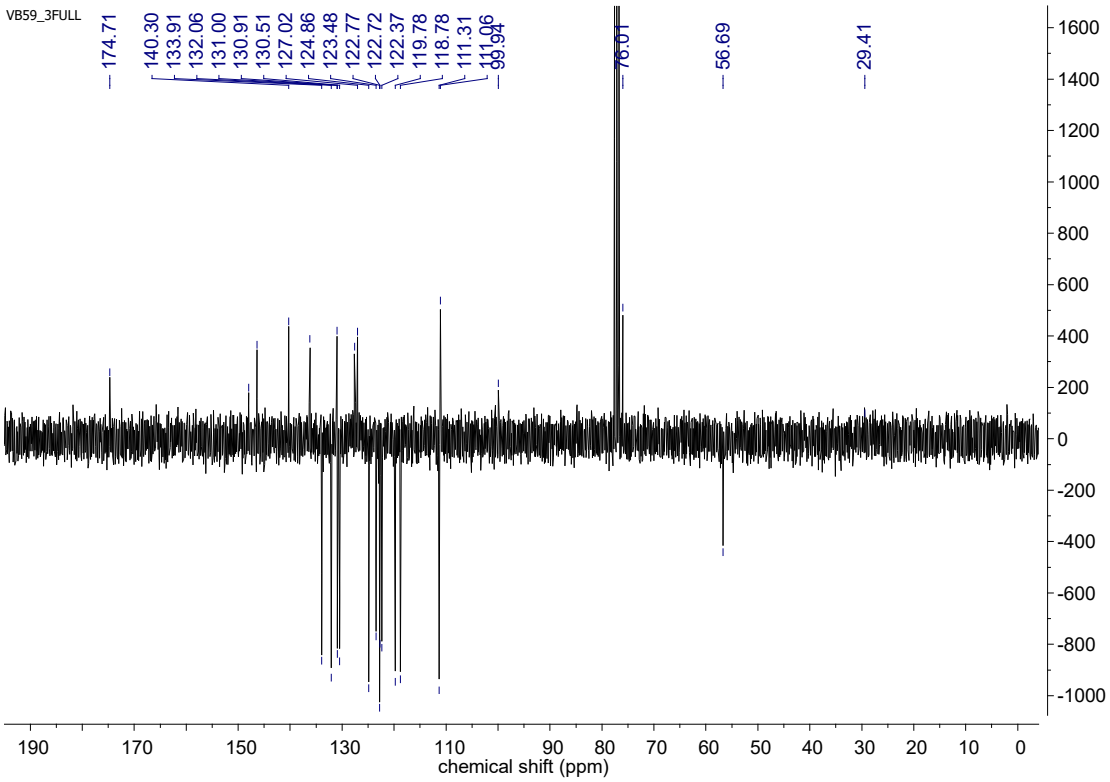
(3*R*,9b*S*)-3-((1*H*-indol-3-yl)methyl)-9b-(4-methoxyphenyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 33. Following the general procedure for cyclocondensation reactions, to a solution of (*R*)-tryptophanol (0.0478 g, 0.251 mmol) in toluene (2.5 mL) was added 2-(4-methoxybenzoyl)benzoic acid (0.0541 g, 0.211 mmol). Reaction time: 16 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 1:1. The product was obtained as a white solid (0.0420 g, 40.7%). Mp: 73-76 °C; $[\alpha]^{20}_D$ = -151.0° (c = 0.080, CH_2Cl_2). The ^{1}H NMR was found comparable to the one of compound **22**. MS (ESI) m/z calcd for $C_{26}H_{22}N_2O_3$: 410.2, found 411 $[M+H]^+$.

(3*R*,9b*S*)-3-((1*H*-indol-3-yl)methyl)-9b-(*p*-tolyl)-2,3-dihydrooxazolo[2,3-*a*]isoindol-5(9b*H*)-one 34. Following the general procedure for cyclocondensation reactions, to a solution of (*R*)-tryptophanol (0.114 g, 0.598 mmol) in toluene (5 mL) was added 2-(4-methylbenzoyl)benzoic acid (0.172 g, 0.717 mmol). Reaction time: 17 hours. Eluent for flash chromatography: ethyl acetate/ *n*-hexane, 6:4. The product was obtained as a white solid (0.192 g, 82.5%). Mp: 154-156 °C; $[\alpha]^{20}_D$ = -171.4° (c = 0.11, CH_2Cl_2); The ^{1}H NMR spectrum was found identical to the one of compound **23**. MS (ESI) m/z calcd for $C_{26}H_{22}N_2O_2$: 394.2, found 395 $[M+H]^+$.

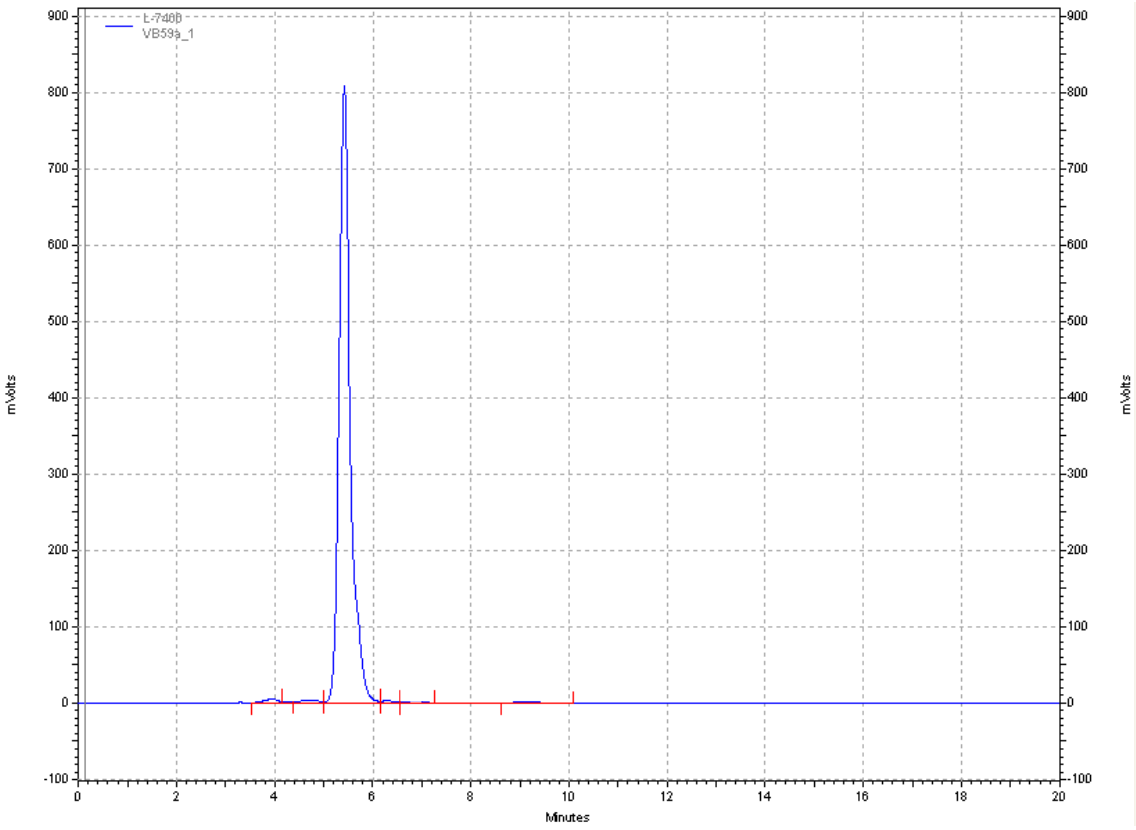
^{1}H NMR spectrum of compound 32 in $CDCl_3$



APT NMR spectrum of compound 32 in $CDCl_3$



HPLC of compound 32 in 70:30 ACN:H_2O



L-7400 Results

Retention Time	Area	Area %	Height	Height %
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4,676	117876	0,89	4507	0,54
5,418	12727397	96,61	808621	97,57
6,293	52448	0,40	3208	0,39
6,890	89663	0,68	4191	0,51
9,156	73960	0,56	2523	0,30

Totals				
	13173820	100,00	828746	100,00

Molecular docking simulations: function scores of compounds 1 and 32

Compound	FRED Chemgauss4 score
1	-11.381303
32	-12.232264