Donepezil+Chromone+Melatonin Hybrids as Promising Agents for Alzheimer’s Disease Therapy

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Synthesis

**Amines synthesis (10 and 11):**

Scheme for 10 synthesis. *Reagents and conditions*¹: (a) (EtO)$_2$P(O)CH$_2$CO$_2$Et, THF, K$_2$CO$_3$, reflux, 1h; (b) (i) H$_2$, Pd/C 10%, PtO$_2$, 4N HCl in dioxane, EtOH, room temp, O.N. (ii) MeOH; (c) BnBr, Et$_3$N, CH$_2$Cl$_2$, O.N.; (d) LiAlH$_4$, dry THF, reflux, 2h; (e) SOCl$_2$, CH$_2$Cl$_2$, reflux, 3h; (f) NH$_3$/MeOH 7M, 5mbarr, 5h.

Scheme for 11 synthesis. *Reagents and conditions*¹: (a) (EtO)$_2$P(O)CH$_2$CH=CHCO$_2$Et, EtOH, NaH, Reflux, 1h; (b) H$_2$, Pd/C 10%, 40mbarr, EtOH, RT O.N.; (c) BnBr, Et$_3$N, CH$_2$Cl$_2$, O.N.; (d) LiAlH$_4$, dry THF, reflux, 2h; (e) SOCl$_2$, CH$_2$Cl$_2$, reflux, 3h; (f) NH$_3$/MeOH 7M, 5mbarr, 5h.

4-(1-benzylpiperidin-4-yl)propan-1-amine (10).

**10** C$_{15}$H$_{24}$N$_2$

**MW:** 232.194 g/mol
10 was synthesized starting from \textit{1-benzyl-4-(3-chlorobutyl)piperidine} 10f which, in turn, was prepared in five steps as described by Choi et al\textsuperscript{1} and Bolea et al\textsuperscript{2}. 10f (1 Eq., 8 mmol, 2014.00 mg) was dissolved in a solution of ammonia 7N in MeOH (24.8 mL) and stirred at 120°C under pressure 15 bar for 5h. After that time, the crude was cooled, evaporated, neutralized by addition of 100 mL of K\textsubscript{2}CO\textsubscript{3} 10% solution and stir for 15 minutes. Then, it was extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and reduced under pressure conditions to afford 1783 mg of 10 (96%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.30 (d, \( J = 4.8 \) Hz, 4H), 7.23 (s, 1H), 3.47 (d, \( J = 1.7 \) Hz, 2H), 2.86 (d, \( J = 11.3 \) Hz, 2H), 2.62 (d, \( J = 47.7 \) Hz, 1H), 1.91 (t, \( J = 10.8 \) Hz, 2H), 1.64 (d, \( J = 9.3 \) Hz, 2H), 1.51 – 1.37 (m, 2H), 1.30 – 1.18 (m, 6H).

\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \( \delta \) 138.74, 129.34, 128.21, 126.95, 63.68, 54.08, 35.83, 34.46, 33.98, 32.57, 27.56.

\textbf{4-(1-benzylpiperidin-4-yl)butan-1-amine (11).}

\begin{center}
\includegraphics[width=0.2\textwidth]{11}
\end{center}

\textbf{11} C\textsubscript{16}H\textsubscript{26}N\textsubscript{2}  
MW: 246.209 g/mol

11 was synthesized starting from \textit{1-benzyl-4-(3-chloropropyl)piperidine} 11f which, in turn, was prepared in five steps as described by Choi et al\textsuperscript{1} and Bolea et al\textsuperscript{2}. 11f (1 Eq., 4.41 mmol, 1086 mg) was dissolved in a solution of ammonia 7N in MeOH (10 mL) and stirred at 120°C under pressure 15 bar for 5h. After that time, the crude was cooled, evaporated, neutralized by addition of 100 mL of K\textsubscript{2}CO\textsubscript{3} 10% solution and stir for 15 minutes. Then, it was extracted with CH\textsubscript{2}Cl\textsubscript{2}, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered and reduced under pressure conditions to afford 1031 mg of 11 (95%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.30 (d, \( J = 4.3 \) Hz, 4H), 7.26 – 7.20 (m, 1H), 3.47 (d, \( J = 2.0 \) Hz, 1H), 2.86 (d, \( J = 10.5 \) Hz, 2H), 2.67 (t, \( J = 6.9 \) Hz, 1H), 2.58 (t, \( J = 6.9 \) Hz, 1H), 1.96
– 1.86 (m, 2H), 1.67 – 1.57 (m, J = 11.4 Hz, 3H), 1.51 – 1.38 (m, 2H), 1.29 (d, J = 12.1 Hz, 2H), 1.26 – 1.15 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 138.72, 129.39, 128.25, 127.00, 63.71, 54.13, 50.09, 42.39, 36.63, 36.61, 35.87, 35.81, 32.54, 32.53, 24.71, 24.23.

General Procedure A (Synthesis of isocyanides 4-7):

Scheme for isocyanides (4-7) synthesis. Reagents and conditions: (a) Ethyl formate, reflux, 4h; (b) Burgess reagent, dry CHCl$_3$, 1h.

General procedure A.1 – Synthesis of N-formamides derivatives (4a-7a).
Tryptamine derivative (1 Eq.) was dissolved in ethyl formate (4 Eq.). The mixture was refluxed at 70°C for 4h. The crude was then poured into 2N HCl solution and extracted three times with CH$_2$Cl$_2$. Organic layers were joined, washed with NaOH 5% solution, dried over Na$_2$SO$_4$, filtered, and concentrated under pressure conditions, to afford corresponding formamide with yields from 91 to 99%.

General procedure A.2 – Synthesis of isocyanides derivatives (4-7).
Commercially available burgess reagent (1.5 Eq.) was added to a solution of corresponding N-formamide derivative, synthesized from general procedure A.1 (1 Eq.), in freshly distilled CH$_2$Cl$_2$ (1 mL/mmol) under argon. The resulting mixture was heated to reflux at 60°C for 1h preserving anhydride conditions. After that, the crude was poured into 20 mL of CH$_2$Cl$_2$, washed twice with water, dried over Na$_2$SO$_4$, filtered and concentrated under pressure conditions to be purified by flash column chromatography at 100% CH$_2$Cl$_2$, affording yields from 51 to 59%.
**N-(2-(1H-indol-3-yl)ethyl)formamide (4a).**

The crude was prepared according to *general procedure A.1*, starting from commercially available tryptamine (1 Eq., 12.48 mmol, 2000 mg) that was suspended in ethyl formate (3.97 Eq., 49.51 mmol, 4 mL) to afford 2228.93 mg of 4a as a dark brown oil (95%). The crude was used for the synthesis of 4 without further purification.

**N-(2-(5-methoxy-1H-indol-3-yl)ethyl)formamide (5a).**

The crude was prepared according to *general procedure A.1*, starting from commercially available 5-methoxytryptamine (1 Eq., 10.51 mmol, 2000 mg) that was suspended in ethyl formate (4.7 Eq., 49.51 mmol, 4 mL) to afford 2130.03 mg of 5a as a light brown powder (93%). The crude was used for the synthesis of 5 without further purification.
*N-(2-(5-isopropoxy-1H-indol-3-yl)ethyl)formamide (6a).*

![Chemical structure of 6a](image)

**6a** \(\text{C}_{14}\text{H}_{18}\text{N}_{2}\text{O}_{2}\)  
**MW:** 246.105 g/mol

6a was prepared according to *general procedure A.1* starting from 5-isopropoxytryptamine, which in turn was synthesized as described by Choi et al.1 and Benchekroun et al.3. 5-isopropoxytryptamine (1 Eq., 6.03 mmol, 1400 mg) was suspended in ethyl formate (4.7 Eq., 49.51 mmol, 4 mL) to afford 1452.50 mg of 6a as dark brown oil (92%). The crude was used for the synthesis of 6 without further purification.

*N-(2-(5-propoxy-1H-indol-3-yl)ethyl)formamide (7a).*

![Chemical structure of 7a](image)

**7a** \(\text{C}_{14}\text{H}_{18}\text{N}_{2}\text{O}_{2}\)  
**MW:** 246.105 g/mol

7a was prepared according to *general procedure A.1*, starting from 5-propoxytryptamine, which in turn was synthesized as described in by Choi et al.1 and Benchekroun et al.3. 5-propoxytryptamine (1 Eq., 2.99 mmol, 652 mg) was suspended in ethyl formate (4.7 Eq., 49.51 mmol, 4 mL) to afford 675 mg of 7a as a light brown powder (91%). The crude was used for the synthesis of 7 without further purification.
3-(2-isocyanoethyl)-1H-indole (4)

The crude was prepared according to general procedure A.2. Starting from 4a (1 Eq., 11.85 mmol, 2228.93 mg) and burgess reagent (1.5 Eq., 17.78 mmol, 4837.93 mg), 4 was afforded as a light brown powder (1248.20 mg, 56%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.09 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.19 – 7.10 (m, 2H), 3.72 – 3.63 (m, 2H), 3.23 – 3.12 (m, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.15, 136.37, 126.88, 122.71, 122.53, 119.87, 118.32, 111.54, 111.22, 42.47, 25.97.

3-(2-isocyanoethyl)-5-methoxy-1H-indole (5)

The crude was prepared according to general procedure A.2. Starting from 5a (1Eq., 9.77 mmol, 2130.03 mg) and burgess reagent (1.5 Eq., 15.65 mmol, 3491.60 mg), 5 was afforded as a light brown powder. (1153.16 mg, 59%)

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.98 (s, 1H), 7.28 (d, J = 8.8 Hz, 1H), 7.12 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.89 (dd, J = 8.8, 2.4 Hz, 1H), 3.87 (s, 3H), 3.69 – 3.62 (m, 2H), 3.14 (dd, J = 9.7, 4.4 Hz, 2H).
$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.2, 154.43, 131.57, 127.39, 123.56, 112.69, 112.37, 110.97, 100.37, 77.58, 77.26, 76.94, 56.19, 42.47, 26.06.

3-(2-isocyanooethyl)-5-isopropoxy-1H-indole (6)

![Structure of 3-(2-isocyanooethyl)-5-isopropoxy-1H-indole (6)]

6 C$_{14}$H$_{16}$N$_2$O

MW: 228.130 g/mol

The crude was prepared according to general procedure A.2. Starting from 6a (1 Eq., 5.90 mmol, 1452.50 mg) and burgess reagent (1.5 Eq., 8.85 mmol, 2109.61 mg), 6 was afforded as a dark brown oil (794.37, 59%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.03 (s, 1H), 7.26 (d, J = 8.8 Hz, 1H), 7.10 (d, J = 2.3 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.88 (dd, J = 8.8, 2.3 Hz, 1H), 4.55 (dt, J = 12.1, 6.1 Hz, 1H), 3.65 (dd, J = 9.8, 4.3 Hz, 2H), 3.12 (t, J = 7.0 Hz, 2H), 1.37 (d, J = 6.1 Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.03, 152.17, 131.77, 127.42, 123.48, 114.55, 112.12, 110.75, 104.47, 71.59, 42.37, 25.97, 22.37.

3-(2-isocyanooethyl)-5-propoxy-1H-indole (7)

![Structure of 3-(2-isocyanooethyl)-5-propoxy-1H-indole (7)]

7 C$_{14}$H$_{16}$N$_2$O

MW: 228.130 g/mol
The crude was prepared according to general procedure A.2. Starting from 7a (1 Eq., 2.74 mmol, 675 mg) and burgess reagent (1.5 Eq., 4.11 mmol, 980.37 mg), 7 was afforded as a light brown powder (324.02 mg, 51%).

$^1$H NMR (400 MHz, DMSO) $\delta$ 10.73 (s, 1H), 7.23 (d, $J = 8.7$ Hz, 1H), 7.19 (d, $J = 2.4$ Hz, 1H), 7.07 (d, $J = 2.3$ Hz, 1H), 6.72 (dd, $J = 8.7$, 2.4 Hz, 1H), 3.92 (t, $J = 6.6$ Hz, 2H), 3.78 – 3.68 (m, 2H), 3.00 (ddd, $J = 6.8$, 4.9, 2.0 Hz, 2H), 1.79 – 1.68 (m, 2H), 1.00 (t, $J = 7.4$ Hz, 3H).

$^{13}$C NMR (101 MHz, DMSO) $\delta$ 155.38, 152.44, 131.29, 127.13, 124.13, 112.02, 111.73, 109.59, 101.18, 69.45, 42.05, 25.17, 22.31, 10.58.

General Procedure B (Ugi Adducts 14a-14p):

Paraformaldehyde (1 Eq.) was added to a solution of benzylamine (1 Eq.) in CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). The resulting mixture was stirred for 1h at room temperature. Then, 2-chromone-carboxylic acid (1 Eq.) and finally corresponding isocyanide (1 Eq.) were added. The reaction mixture was stirred for 24h at 60°C. The crude product was purified by flash column chromatography to afford the corresponding Ugi adduct.

$N$-(2-((2-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-$N$-((1-benzylpiperidin-4-yl)methyl)-4-oxo-4H-chromene-2-carboxamide (14a).

![Chemical Structure](14a)

14a C$_{35}$H$_{36}$N$_4$O$_4$

MW: 576.274 g/mol

The crude was prepared according to general procedure B starting from commercial l-benzylpiperidin-4-yl)methanamine 8 (204.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1
mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanooethyl)-1H-indole 4 (170.00 mg, 1 mmol) in 10mL of CH₂Cl₂:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH₂Cl₂:MeOH, to afford 14a as a light orange foam (125 mg, 21.69%).

**¹H NMR (400 MHz, CDCl₃)** δ 8.38 (s, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.72 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.47 (dd, J = 13.3, 5.6 Hz, 1H), 7.41 – 7.34 (m, 1H), 7.30 (dd, J = 14.8, 9.3 Hz, 4H), 7.25 – 7.19 (m, 2H), 7.14 (t, J = 7.5 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.41 (s, 1H), 6.13 (d, J = 6.3 Hz, 1H), 3.99 (s, 2H), 3.65 (dd, J = 11.7, 5.8 Hz, 2H), 3.45 (s, 2H), 3.19 (d, J = 7.3 Hz, 2H), 3.01 (t, J = 6.5 Hz, 2H), 2.81 (d, J = 9.5 Hz, 2H), 1.87 (t, J = 10.7 Hz, 2H), 1.74 (s, 1H), 1.68 – 1.59 (m, 1H), 1.49 (d, J = 1.4 Hz, 2H), 1.01 (dd, J = 21.6, 11.3 Hz, 1H).

**¹³C NMR (101 MHz, CDCl₃)** δ 177.46, 167.79, 163.72, 157.59, 155.74, 138.27, 136.65, 135.92, 134.73, 129.30, 128.34, 127.28, 127.18, 126.26, 126.04, 124.38, 122.49, 119.75, 118.76, 118.34, 112.59, 112.23, 111.64, 63.34, 56.29, 53.08, 51.03, 39.65, 34.70, 29.94, 25.05.

**HRMS ESI-TOF [M+H]+ m/z** calcd. for C₃₅H₃₇N₄O₄: 577.2783, found: 577.2809.

N-((1-benzylpiperidin-4-yl)methyl)-N-(2-((2-(5-ethyl-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14b).

The crude was prepared according to **general procedure B** starting from commercial 1-benzylpiperidin-4-yl)methanamine 8 (204.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanooethyl)-5-methoxy-1H-indole 5 (200.00 mg, 1 mmol) in 10mL of CH₂Cl₂:MeOH (1:3 v/v, 0.8 mmol/mL).
After 24h, the crude was purified by flash column at 9:1 CH₂Cl₂:MeOH, to afford 14b as a yellow foam (41 mg, 7%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.23 (s, 1H), 8.18 (d, \(J = 7.8\) Hz, 1H), 7.65 (t, \(J = 7.5\) Hz, 1H), 7.48 (t, \(J = 7.5\) Hz, 1H), 7.39 (d, \(J = 8.3\) Hz, 1H), 7.29 (d, \(J = 9.4\) Hz, 2H), 7.25 – 7.15 (m, 4H), 6.99 (d, \(J = 14.3\) Hz, 2H), 6.81 (dd, \(J = 8.8, 2.1\) Hz, 1H), 6.42 (s, 1H), 6.12 (t, \(J = 6.3\) Hz, 1H), 4.01 (s, 2H), 3.84 (s, 3H), 3.64 (dd, \(J = 11.9, 5.9\) Hz, 2H), 3.46 (s, 2H), 3.21 (d, \(J = 7.2\) Hz, 2H), 2.98 (t, \(J = 6.5\) Hz, 2H), 2.82 (d, \(J = 9.2\) Hz, 2H), 1.89 (t, \(J = 11.0\) Hz, 2H), 1.77 – 1.61 (m, 2H), 1.51 (d, \(J = 13.1\) Hz, 2H), 1.03 (dd, \(J = 21.7, 11.7\) Hz, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 177.45, 167.79, 163.73, 157.55, 155.74, 154.27, 138.46, 134.73, 131.77, 129.30, 128.35, 127.71, 127.20, 126.26, 126.05, 124.39, 123.21, 118.36, 114.21, 112.62, 100.63, 63.31, 56.31, 56.03, 53.08, 51.08, 39.52, 34.72, 29.94, 25.06.

HRMS ESI-TOF [M+H]+ m/z calcld. for C\(_{36}\)H\(_{39}\)N\(_4\)O\(_5\): 607.2915, found: 607.2888.

N-((1-benzylpiperidin-4-yl)methyl)-N-(2-((2-(5-isopropoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14c).

\begin{center}
\includegraphics[width=0.3\textwidth]{14c.png}
\end{center}

14c C\(_{38}\)H\(_{42}\)N\(_4\)O\(_5\)

MW: 634.316 g/mol

The crude was prepared according to general procedure B starting from commercial 1-benzylpiperidin-4-yl)methanamine 8 (204.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-5-isopropoxy-1H-indole 6 (228.00 mg, 1 mmol) in 10mL of CH\(_2\)Cl\(_2\):MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH\(_2\)Cl\(_2\):MeOH, to afford 14c as a yellow foam (104.30 mg, 16.44%).
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 8.28 – 8.11 (m, \(J = 7.8\) Hz, 2H), 7.66 (t, \(J = 7.8\) Hz, 1H), 7.48 (t, \(J = 7.5\) Hz, 1H), 7.44 – 7.37 (m, 1H), 7.36 – 7.27 (m, 3H), 7.25 – 7.15 (m, 3H), 7.09 – 6.97 (m, 2H), 6.81 (dd, \(J = 8.7, 2.2\) Hz, 1H), 6.39 – 6.28 (m, 2H), 4.56 – 4.46 (m, 1H), 4.00 (s, 2H), 3.63 (dd, \(J = 11.9, 6.0\) Hz, 2H), 3.44 (s, 2H), 3.22 (d, \(J = 7.4\) Hz, 2H), 2.96 (t, \(J = 6.5\) Hz, 2H), 2.76 (d, \(J = 10.2\) Hz, 2H), 1.85 (t, \(J = 10.6\) Hz, 2H), 1.71 – 1.62 (m, 1H), 1.47 (d, \(J = 10.1\) Hz, 2H), 1.33 (d, \(J = 6.1\) Hz, 7H), 1.10 – 0.99 (m, \(J = 11.8\) Hz, 1H).

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta \) 177.50, 167.75, 163.71, 157.59, 155.75, 152.15, 135.92, 134.76, 132.08, 129.33, 128.36, 127.82, 126.27, 126.04, 124.37, 123.25, 120.54, 118.38, 114.60, 112.24, 112.18, 104.76, 71.42, 71.27, 63.27, 56.28, 53.06, 51.05, 39.48, 34.69, 29.84, 25.09, 22.43, 22.38.

HRMS ESI-TOF [M+H]+ \(m/z\) calc. for C\(_{38}\)H\(_{42}\)N\(_4\)O\(_5\): 635.3228, found: 635.3210.

\(N\)-(1-benzylpiperidin-4-yl)methyl)-4-oxo-N-(2-oxo-2-(2-(5-propoxy-1H-indol-3-yl)ethyl)amino)ethyl)-4H-chromene-2-carboxamide (14d).

\[
\text{14d } \text{C}_{38}\text{H}_{42}\text{N}_{4}\text{O}_{5} \\
\text{MW: } 634.316 \text{ g/mol}
\]

The crude was prepared according to general procedure B starting from commercial 1-benzylpiperidin-4-yl)methanamine 8 (204.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-5-propoxy-1H-indole 7 (228.00 mg, 1 mmol) in 10mL of CH\(_2\)Cl\(_2\):MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH\(_2\)Cl\(_2\):MeOH, to afford 14d as a gold foam (96 mg, 15.13%).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 8.18 (d, \(J = 7.7\) Hz, 1H), 8.11 (s, 1H), 7.66 (t, \(J = 7.6\) Hz, 1H), 7.48 (t, \(J = 7.6\) Hz, 1H), 7.39 (d, \(J = 8.4\) Hz, 1H), 7.34 – 7.27 (m, 3H), 7.25 – 7.16 (m,
J = 14.3, 8.6 Hz, 3H), 6.99 (d, J = 16.2 Hz, 2H), 6.82 (dd, J = 8.8, 2.2 Hz, 3H), 3.69 – 3.60 (m, 2H), 3.41 (s, 1H), 3.20 (d, J = 7.0 Hz, 2H), 2.97 (t, J = 6.5 Hz, 2H), 2.81 (d, J = 9.1 Hz, 2H), 1.91 – 1.76 (m, 4H), 1.70 – 1.60 (m, 2H), 1.60 – 1.51 (m, 1H), 1.46 (d, J = 12.2 Hz, 2H), 1.05 (t, J = 7.4 Hz, 4H).

**13C NMR (101 MHz, CDCl₃)** \(\delta\) 177.48, 167.77, 163.72, 157.56, 155.75, 153.75, 134.74, 131.79, 129.30, 128.35, 127.72, 127.19, 126.27, 126.05, 124.39, 123.17, 118.36, 113.15, 112.29, 101.79, 70.53, 63.31, 56.28, 53.08, 51.05, 39.49, 34.72, 29.94, 29.85, 25.06, 22.97, 10.80.

**HRMS ESI-TOF** [M+H]+ \(m/z\) calcd. for C₃₈H₄₃N₄O₅: 635.3228, found: 635.3211.

\[ \text{N-(2-((2-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-N-(2-(1-benzylpiperidin-4-yl)ethyl)-4-oxo-4H-chromene-2-carboxamide (14e).} \]

\[ \text{14e C}_{38}\text{H}_{38}\text{N}_{4}\text{O}_{4} \]

MW: 590.289 g/mol

The crude was prepared according to **general procedure B** starting from commercial 4-(2-aminoethyl)-1-benzylpiperidine 9 (436.68 mg, 2 mmol), paraformaldehyde 13 (60 mg, 2 mmol), 2-chromone-carboxylic acid 12 (380.2 mg, 2 mmol) and 3-(2-isocyanatoethyl)-1H-indole 4 (340 mg, 2 mmol) in 10mL of CH₂Cl₂:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH₂Cl₂:MeOH, to afford 14e as a light yellow powder (391 mg, 33.11%).

**1H NMR (400 MHz, CDCl₃)** \(\delta\) 8.73 – 8.44 (m, 1H), 8.16 (d, J = 7.4 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 7.58 (d, J = 7.6 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.35 (d, J = 8.6 Hz, 1H), 7.33 – 7.26 (m, J = 13.4 Hz, 4H), 7.24 – 7.21 (m, 1H), 7.19 – 6.95 (m, 4H), 6.48 (s, 1H), 6.18 (t, J = 6.2 Hz, 1H), 3.96 (s, 2H), 3.71 – 3.62 (m, J = 17.9, 11.9 Hz, 2H), 3.42 (s, 1H), 3.30 – 3.19 (m,
2H), 3.01 (t, J = 6.3 Hz, 2H), 2.83 (d, J = 10.6 Hz, 2H), 1.99 (s, 1H), 1.82 (t, J = 10.8 Hz, 1H), 1.59 – 1.51 (m, J = 8.2 Hz, 2H), 1.42 (s, 4H), 1.26 (s, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.49, 167.68, 163.17, 157.63, 155.57, 138.32, 136.60, 134.73, 129.31, 128.30, 127.39, 127.13, 126.20, 126.03, 124.31, 122.48, 122.30, 119.60, 118.71, 118.21, 112.50, 112.10, 111.61, 63.44, 53.65, 50.22, 48.54, 39.67, 35.07, 32.06, 25.03.

HRMS ESI-TOF [M+H]$^+$ m/z calcd. for C$_{37}$H$_{39}$N$_4$O$_4$: 591.2966, found: 591.2954.

$N$-(2-(1-benzylpiperidin-4-yl)ethyl)-$N$-(2-((2-(5-methoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14f).

The crude was prepared according to general procedure B starting from commercial 4-(2-aminoethyl)-1-benzylpiperidine 9 (436.68 mg, 2 mmol), paraformaldehyde 13 (60 mg, 2 mmol), 2-chromone-carboxylic acid 12 (380.2 mg, 2 mmol) and 3-(2-isocyanoethyl)-5-methoxy-1H-indole 5 (400 mg, 2 mmol) in 10 mL of CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). After 24 h, the crude was purified by flash column at 9:1 CH$_2$Cl$_2$:MeOH, to afford 14f as a gold foam (92 mg, 14.82%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.37 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.66 (t, J = 50.0, 7.2 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.33 – 7.27 (m, 4H), 7.24 – 7.11 (m, 2H), 7.07 – 6.93 (m, 2H), 6.80 (dd, J = 8.8, 2.3 Hz, 1H), 6.47 (s, 1H), 6.10 (t, J = 6.2 Hz, 1H), 3.98 (s, 2H), 3.82 (s, 3H), 3.73 – 3.61 (m, 2H), 3.52 – 3.48 (m, 1H), 3.43 (s, 1H), 3.30 – 3.22 (m, 2H), 3.04 – 2.95 (m, 2H), 2.84 (d, J = 10.5 Hz, 2H), 1.95 (s, 1H), 1.88 – 1.76 (m, 3H), 1.63 – 1.52 (m, 2H), 1.43 (d, J = 11.3 Hz, 1H), 1.20 – 1.09 (m, 2H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.48, 167.73, 163.22, 157.58, 155.61, 154.24, 138.29, 134.74, 131.75, 129.33, 128.32, 127.80, 127.15, 126.24, 126.09, 124.37, 123.22, 118.24, 112.50, 112.34, 112.27, 112.14, 100.67, 63.44, 56.03, 53.64, 50.42, 48.63, 39.49, 35.14, 33.64, 32.08, 25.04.

HRMS ESI-TOF [M+H]+$^+$ m/z calcd. for C$_{37}$H$_{41}$N$_4$O$_5$: 621.3071 , found: 621.3058.

N-(2-(1-benzylpiperidin-4-y)ethyl)-N-(2-((5-isoproxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14g).

\[
\text{14g C}_{39}\text{H}_{44}\text{N}_4\text{O}_5 \\
\text{MW: 648.331 g/mol}
\]

The crude was prepared according to general procedure B starting from commercial 4-(2-aminoethyl)-1-benzylpiperidine 9 (436.68 mg, 2 mmol), paraformaldehyde 13 (60 mg, 2 mmol), 2-chromone-carboxylic acid 12 (380.2 mg, 2 mmol) and 3-(2-isocyanoethyl)-5-isoproxy-1H-indole 6 (456 mg, 2 mmol) in 10mL of CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH$_2$Cl$_2$:MeOH, to afford 14g as a light yellow foam (227 mg, 17.51%).

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.39 (s, 1H), 8.18 (d, J = 7.6 Hz, 1H), 7.65 (t, J = 7.0 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 10.0 Hz, 1H), 7.31 – 7.27 (m, 4H), 7.24 – 7.10 (m, 2H), 7.08 – 6.91 (m, 2H), 6.80 (dd, J = 8.8, 2.2 Hz, 1H), 6.48 (s, 1H), 6.11 (t, J = 6.2 Hz, 1H), 4.49 (m, J = 12.1, 6.1 Hz, 1H), 3.98 (s, 2H), 3.72 – 3.59 (m, 2H), 3.42 (s, 1H), 3.34 – 3.25 (m, 2H), 2.96 (t, J = 6.1 Hz, 2H), 2.83 (d, J = 10.4 Hz, 2H), 1.93 (s, 1H), 1.88 – 1.72 (m, 3H), 1.62 – 1.52 (m, 2H), 1.51 – 1.40 (m, 2H), 1.32 (d, J = 5.9 Hz, 7H), 1.17 – 1.09 (m, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.39, 167.59, 163.11, 157.52, 155.52, 152.03, 138.29, 134.64, 131.95, 129.24, 128.20, 127.77, 127.02, 126.11, 125.97, 124.26, 123.14,
118.16, 114.46, 112.07, 104.76, 63.37, 50.26, 48.52, 39.37, 35.06, 33.52, 32.02, 24.97, 22.31.

HRMS ESI-TOF [M+H]+ m/z calcd. for C_{39}H_{45}N_4O_5: 649.3384, found: 649.3365.

N-(2-(1-benzylpiperidin-4-yl)ethyl)-4-oxo-N-(2-oxo-2-((2-(5-propoxy-1H-indol-3-yl)ethyl)amino)ethyl)-4H-chromene-2-carboxamide (14h).

The crude was prepared according to general procedure B starting from commercial 4-(2-aminoethyl)-1-benzylpiperidine 9 (436.68 mg, 2 mmol), paraformaldehyde 13 (60 mg, 2 mmol), 2-chromone-carboxylic acid 12 (380.2 mg, 2 mmol) and 3-(2-isocyanoethyl)-5-propoxy-1H-indole 7 (456 mg, 2 mmol) in 10mL of CH_2Cl_2:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH_2Cl_2:MeOH, to afford 14h as a light yellow foam (92.0 mg, 7.1%).

^1H NMR (400 MHz, CDCl_3) δ 8.37 (s, 1H), 8.18 (d, J = 7.1 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.34 – 7.27 (m, 3H), 7.23 – 7.11 (m, 2H), 6.99 (d, J = 15.1 Hz, 2H), 6.80 (d, J = 8.6 Hz, 1H), 6.47 (s, 1H), 6.10 (t, J = 6.2 Hz, 1H), 4.03 (s, 1H), 3.93 (t, J = 6.5 Hz, 3H), 3.76 – 3.61 (m, 2H), 3.42 (s, 1H), 3.31 – 3.21 (m, 2H), 2.98 (d, J = 6.1 Hz, 2H), 2.83 (d, J = 10.2 Hz, 2H), 1.94 (s, 1H), 1.80 (q, J = 17.5, 10.5 Hz, 4H), 1.75 (d, J = 5.0 Hz, 1H), 1.63 – 1.51 (m, J = 16.3 Hz, 2H), 1.51 – 1.39 (m, 2H), 1.29 – 1.24 (m, 1H), 1.13 (d, J = 8.9 Hz, 1H), 1.04 (t, J = 7.4 Hz, 3H).

^13C NMR (101 MHz, CDCl_3) δ 177.40, 167.60, 163.11, 157.50, 155.51, 153.61, 138.24, 134.64, 131.66, 129.22, 128.21, 127.69, 127.04, 126.13, 125.97, 124.26, 123.08,
118.15, 112.96, 112.15, 112.09, 112.02, 101.72, 70.46, 63.36, 53.46, 50.27, 48.51, 39.33, 35.05, 33.51, 31.99, 24.93, 22.85, 10.68.

**HRMS ESI-TOF [M+H]+ m/z**

calcd. for C_{39}H_{45}N_{4}O_{5}: 649.3384, found: 649.3369.

\[
N-(2-((2-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-N-(3-(1-benzylpiperidin-4-yl)propyl)-4-oxo-4H-chromene-2-carboxamide (14i).
\]

![Chemical Structure](image)

**14i** C_{37}H_{40}N_{4}O_{4}

MW: 604.305 g/mol

The crude was prepared according to **general procedure B** starting from 4-(1-benzylpiperidin-4-yl)propan-1-amine 10 (232.16 mg, 1 mmol), paraformaldehyde 13 (300. mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-1H-indole 4 (170.24 mg, 1 mmol) in 10mL of CH_{2}Cl_{2}:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH_{2}Cl_{2}:MeOH, to afford 14i as a yellow foam (57 mg, 9.43%).

**^1H NMR (400 MHz, CDCl_{3})**

δ 8.51 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.69 (t, J = 7.7 Hz, 1H), 7.56 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.35 – 7.21 (m, 7H), 7.14 (t, J = 7.5 Hz, 1H), 7.11 – 7.04 (m, 2H), 6.48 (s, 1H), 6.09 (s, 1H), 3.99 (s, 2H), 3.67 (dd, J = 12.0, 6.1 Hz, 2H), 3.47 (s, 2H), 3.24 (t, J = 3.2 Hz, 2H), 3.02 (t, J = 6.4 Hz, 2H), 2.84 (d, J = 11.1 Hz, 2H), 1.89 (t, J = 7.7 Hz, 2H), 1.71 – 1.55 (m, 3H), 1.51 (d, J = 10.7 Hz, 2H), 1.24 – 1.13 (m, 3H), 1.12 – 1.02 (m, J = 12.6 Hz, 1H).

**^13C NMR (101 MHz, CDCl_{3})**

δ 177.51, 167.81, 163.24, 157.66, 155.59, 138.30, 136.61, 134.75, 129.47, 128.33, 127.42, 127.17, 126.20, 126.07, 124.39, 122.38, 119.65, 118.75, 118.17, 112.57, 112.16, 111.59, 63.62, 53.81, 51.04, 50.63, 39.60, 35.32, 33.25, 32.04, 25.70, 25.06.

**HRMS ESI-TOF [M+H]+ m/z**

calcd. for C_{37}H_{41}N_{4}O_{4}: 605.3122, found: 605.3105.
N-(3-(1-benzylpiperidin-4-yl)propyl)-N-(2-(2-(5-methoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14j).

The crude was prepared according to general procedure B starting from 4-(1-benzylpiperidin-4-yl)propan-1-amine 10 (232.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-5-methoxy-1H-indole 5 (200.04 mg, 1 mmol) in 10mL of CH_{2}Cl_{2}:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH_{2}Cl_{2}:MeOH, to afford 14j as a yellow foam (14 mg, 2.21%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.40 (s, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.64 (t, $J = 7.5$ Hz, 1H), 7.46 (t, $J = 7.4$ Hz, 1H), 7.34 – 7.21 (m, 6H), 7.18 (d, $J = 8.9$ Hz, 1H), 7.03 (d, $J = 22.5$ Hz, 2H), 6.80 (dd, $J = 8.8$, 2.2 Hz, 1H), 6.48 (s, 1H), 6.11 (s, 1H), 4.00 (s, 2H), 3.82 (s, 3H), 3.66 (dd, $J = 12.0$, 6.0 Hz, 2H), 3.46 (s, 2H), 3.26 (d, $J = 3.2$ Hz, 2H), 2.98 (t, $J = 6.3$ Hz, 2H), 2.84 (d, $J = 11.1$ Hz, 2H), 1.86 (t, $J = 14.3$ Hz, 2H), 1.64 – 1.47 (m, 5H), 1.19 – 1.13 (m, 2H), 1.12 – 1.03 (m, $J = 6.7$ Hz, 2H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.49, 167.83, 163.25, 157.62, 155.60, 154.23, 138.40, 134.74, 131.73, 129.45, 129.36, 128.33, 127.83, 127.14, 126.21, 126.07, 124.40, 123.11, 118.17, 112.52, 112.31, 112.25, 112.20, 100.59, 63.66, 56.01, 53.83, 51.12, 50.72, 39.48, 35.34, 33.25, 32.07, 25.71, 25.05.

HRMS ESI-TOF [M+H]+$^+$ m/z calcd. for C$_{38}$H$_{42}$N$_4$O$_5$: 635.3228, found: 635.3210.

N-(3-(1-benzylpiperidin-4-yl)propyl)-N-(2-(2-(5-isopropoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14k).
The crude was prepared according to **general procedure B** starting from 4-\((1\text{-benzylpiperidin-4-yl})\text{propan-1-amine} \) 10 (173.00 mg, 1 mmol), paraformaldehyde 13 (22.15 mg, 0.75 mmol), 2-chromone-carboxylic acid 12 (142.6 mg, 0.75 mmol) and 3-(2-isocyanoethyl)-5-isoproxy-\(1H\text{-indole} \) 6 (170.00 mg, 0.75 mmol) in 10mL of \(\text{CH}_2\text{Cl}_2:\text{MeOH} \) (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 \(\text{CH}_2\text{Cl}_2:\text{MeOH} \), to afford 14k as a orange foam (14 mg, 2.82%).

\[ 1^H \text{NMR (400 MHz, CDCl}_3\text{)} \delta 8.35 (s, 1H), 8.21 (d, J = 7.5 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.35 – 7.28 (m, 6H), 7.19 (d, J = 8.7 Hz, 1H), 7.08 – 6.92 (m, 2H), 6.77 (d, J = 9.0 Hz, 1H), 6.49 (s, 1H), 6.07 (t, 1H), 4.53 – 4.45 (m, 1H), 4.01 (s, 2H), 3.69 – 3.59 (m, 2H), 3.51 – 3.44 (m, J = 5.9 Hz, 2H), 3.34 – 3.20 (m, 2H), 3.00 – 2.94 (m, 2H), 2.85 (d, J = 8.6 Hz, 2H), 1.99 – 1.83 (m, J = 36.6 Hz, 2H), 1.52 (d, J = 10.8 Hz, 4H), 1.31 (d, J = 6.0 Hz, 7H), 1.14 – 1.03 (m, 3H).

\[ 13^C \text{NMR (101 MHz, CDCl}_3\text{)} \delta 177.39, 167.42, 163.26, 157.64, 155.32, 152.11, 138.46, 134.77, 132.04, 129.53, 128.39, 127.92, 127.28, 126.21, 126.06, 125.24, 123.14, 118.19, 118.03, 113.35, 112.17, 104.79, 71.45, 63.52, 53.77, 51.06, 50.65, 39.47, 35.32, 33.47, 32.16, 29.85, 25.09, 24.92, 22.41.

\[ \text{HRMS ESI-TOF [M+H]}+ \text{ m/z calcd. for C}_{40}\text{H}_{46}\text{NaO}_{5}: 663.3541, \text{found: 663.3522.} \]

\[ N-(3-(1\text{-benzylpiperidin-4-yl})\text{propyl})-4\text{-oxo-N-((2-oxo-2-((2-(5-propoxy-1H-indol-3-yl)}\text{ethyl})amino)ethyl})-4H\text{-chromene-2-carboxamide (14l).} \]
14l $\text{C}_{40}\text{H}_{46}\text{N}_{4}\text{O}_{5}$

MW: 662.331 g/mol

The crude was prepared according to general procedure B starting from 4-(1-benzylpiperidin-4-yl)propan-1-amine 10 (232.16 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanatoethyl)-5-propoxy-1H-indole 7 (228.00 mg, 1 mmol) in 10mL of CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH$_2$Cl$_2$:MeOH, to afford 14j as a light brown foam (23 mg, 3.47%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.41 (s, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.64 (t, J = 8.1 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.35 – 7.21 (m, 6H), 7.17 (d, J = 8.7 Hz, 1H), 6.99 (d, J = 17.0 Hz, 2H), 6.80 (dd, J = 8.6, 1.7 Hz, 1H), 6.48 (s, 1H), 6.13 (s, 1H), 4.00 (s, 2H), 3.91 (t, J = 6.6 Hz, 2H), 3.64 (dd, J = 13.2, 7.5 Hz, 2H), 3.52 – 3.44 (m, 2H), 3.24 (dt, J = 16.4, 9.3 Hz, 2H), 2.97 (t, J = 6.0 Hz, 2H), 2.84 (d, J = 11.2 Hz, 2H), 1.98 – 1.74 (m, 5H), 1.66 – 1.47 (m, 4H), 1.22 – 1.13 (m, 3H), 1.11 – 0.98 (m, 4H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.50, 167.79, 163.22, 157.62, 155.59, 153.68, 138.35, 134.74, 131.75, 129.45, 128.33, 127.84, 127.15, 126.19, 126.04, 124.39, 123.09, 118.17, 113.01, 112.22, 112.16, 101.75, 70.52, 63.63, 53.82, 51.07, 50.65, 39.48, 35.35, 33.25, 32.05, 25.73, 25.03, 22.95, 10.77.

HRMS ESI-TOF [M+H]$^+$ m/z calcd. for C$_{40}$H$_{47}$N$_{4}$O$_{5}$: 663.3541, found: 663.3517.

$N$-(2-((2-(1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-$N$-(4-(1-benzylpiperidin-4-yl)butyl)-4-oxo-4H-chromene-2-carboxamide (14m).
The crude was prepared according to general procedure B starting from 4-((1-benzylpiperidin-4-yl)butan-1-yl)butan-1-amine 11 (246.5 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-1H-indole 4 (170.00 mg, 1 mmol) in 10mL of CH₂Cl₂:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH₂Cl₂:MeOH with NH₃ 1%, to afford 14m as an orange foam (71.4 mg, 11.54%).

**1H NMR (400 MHz, CDCl₃) δ** 8.45 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.70 (dd, J = 16.8, 8.1 Hz, 1H), 7.46 (d, J = 7.1 Hz, 1H), 7.33 (dd, J = 12.2, 6.2 Hz, 7H), 7.21 – 7.11 (m, 2H), 7.10 – 6.96 (m, 2H), 6.49 (s, 1H), 6.13 (s, 1H), 3.95 (s, 2H), 3.72 – 3.60 (m, J = 18.2, 11.5, 6.6 Hz, 2H), 3.52 (t, J = 16.0 Hz, 2H), 3.32 – 3.16 (m, 2H), 3.02 (t, J = 6.3 Hz, 2H), 2.94 – 2.82 (m, 2H), 2.01 – 1.87 (m, 3H), 1.69 – 1.59 (m, 2H), 1.52 (d, J = 12.3 Hz, 3H), 1.12 (s, 5H).

**13C NMR (101 MHz, CDCl₃) δ** 177.70, 167.79, 163.23, 156.33, 155.89, 154.11, 146.88, 136.63, 134.74, 129.88, 129.61, 128.39, 128.15, 127.33, 126.24, 126.08, 124.39, 122.47, 122.37, 119.67, 118.75, 118.75, 112.47, 112.16, 111.64, 63.39, 53.78, 50.57, 39.68, 36.05, 35.49, 31.97, 29.84, 28.80, 25.07, 23.81.

**HRMS ESI-TOF [M+H]+ m/z** calcd. for C₃₈H₄₂N₄O₄: 619.3279, found: 619.3251.

\( N\)-((4-(1-benzylpiperidin-4-yl)butyl)-\( N\)-((2-((5-methoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14n).
The crude was prepared according to general procedure B starting from 4-(1-benzylpiperidin-4-yl)butan-1-amine 11 (203 mg, 0.82 mmol), paraformaldehyde 13 (24.73 mg, 0.82 mmol), 2-chromone-carboxylic acid 12 (166.81 mg, 0.82 mmol) and 3-(2-isocynoethyl)-5-methoxy-1H-indole 5 (164.50 mg, 0.82 mmol) in 10mL of CH₂Cl₂:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH₂Cl₂:MeOH with NH₃ 1%, to afford 14n as a light brown foam (49 mg, 7.55%).

$$\text{1H NMR (400 MHz, CDCl}_3\text{)} \delta 8.20 (s, 2H), 7.65 (t, J = 6.2 \text{ Hz, 1H}), 7.47 (t, J = 7.5 \text{ Hz, 1H}), 7.38 - 7.28 (m, 5H), 7.24 - 7.13 (m, 2H), 7.03 (d, J = 7.1 \text{ Hz, 2H}), 6.80 (dd, J = 8.8, 2.4 \text{ Hz, 1H}), 6.48 (s, 1H), 6.12 (s, 1H), 4.00 (s, 2H), 3.83 (s, 3H), 3.71 - 3.63 (m, 2H), 3.54 (s, 2H), 3.35 - 3.21 (m, 2H), 3.05 - 2.94 (m, J = 13.9, 7.1 \text{ Hz, 2H}), 2.93 - 2.77 (m, 2H), 2.03 - 1.84 (m, 3H), 1.60 - 1.44 (m, J = 12.5 \text{ Hz, 5H}), 1.13 (s, 5H).$$

$$\text{13C NMR (101 MHz, CDCl}_3\text{)} \delta 177.26, 167.81, 163.25, 154.51, 154.24, 152.74, 146.47, 136.72, 134.73, 131.77, 129.51, 128.35, 127.88, 127.23, 126.23, 126.10, 124.84, 123.21, 119.19, 118.21, 112.54, 112.35, 112.18, 100.64, 63.50, 56.04, 53.85, 50.62, 39.51, 36.14, 35.60, 32.29, 32.10, 28.88, 25.07, 23.83.$$

**HRMS ESI-TOF [M+H]+ m/z** calcd. for C₃₉H₄₄N₄O₅: 649.3384, found: 649.3372.
N-(4-(1-benzylpiperidin-4-yl)butyl)-N-(2-((2-(isopropoxy-1H-indol-3-yl)ethyl)amino)-2-oxoethyl)-4-oxo-4H-chromene-2-carboxamide (14o).

![Chemical structure of 14o]

14o C$_{41}$H$_{48}$N$_{4}$O$_{5}$

MW: 677.370 g/mol

The crude was prepared according to general procedure B starting from 4-(1-benzylpiperidin-4-yl)butan-1-amine 11 (246 mg, 1 mmol), paraformaldehyde 13 (30.03 mg, 1 mmol), 2-chromone-carboxylic acid 12 (190.15 mg, 1 mmol) and 3-(2-isocyanoethyl)-5-isopropoxy-1H-indole 6 (218 mg, 1 mmol) in 10mL of CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH$_2$Cl$_2$:MeOH with NH$_3$ 1%, to afford 14o as a gold foam (38 mg, 5.66%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.25 – 8.08 (m, 2H), 7.65 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.34 – 7.27 (m, 4H), 7.25 – 7.15 (m, 2H), 6.99 (s, 2H), 6.81 (dd, J = 8.8, 2.0 Hz, 1H), 6.49 (s, 1H), 6.13 (t, J = 6.2 Hz, 1H), 4.50 (s, 1H), 4.00 (s, 2H), 3.73 – 3.58 (m, J = 6.1 Hz, 2H), 3.55 – 3.44 (m, 2H), 3.36 – 3.25 (m, 2H), 2.96 (t, J = 6.5 Hz, 2H), 2.90 – 2.78 (m, 2H), 1.99 – 1.80 (m, 2H), 1.68 – 1.55 (m, J = 11.8, 5.2 Hz, 3H), 1.52 (d, J = 11.0 Hz, 2H), 1.32 (d, J = 6.0 Hz, 7H), 1.14 (s, 5H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.72, 167.71, 163.23, 155.52, 154.70, 153.02, 146.52, 136.72, 134.73, 131.77, 129.53, 128.35, 127.87, 127.23, 126.08, 124.39, 122.78, 120.00, 119.21, 118.08, 112.26, 112.18, 104.03, 71.43, 63.48, 53.78, 50.54, 39.50, 36.15, 35.60, 32.17, 29.84, 28.87, 25.04, 22.38.

HRMS ESI-TOF [M+H]$^+$ m/z calcd. for C$_{41}$H$_{48}$N$_{4}$O$_{5}$: 677.3697, found: 677.3668.
N-(4-(1-benzylpiperidin-4-yl)butyl)-4-oxo-N-(2-oxo-2-((2-(5-propoxy-1H-indol-3-yl)ethyl)amino)ethyl)-4H-chromene-2-carboxamide (14p).

![Chemical Structure](image-url)

14p C$_{41}$H$_{48}$N$_{4}$O$_{5}$

MW: 677.370 g/mol

The crude was prepared according to general procedure B starting from 4-(1-benzylpiperidin-4-yl)butan-1-amine 11 (250 mg, 1.05 mmol), paraformaldehyde 13 (32.91 mg, 1.05 mmol), 2-chromone-carboxylic acid 12 (208 mg, 1.05 mmol) and 3-(2-isocyanoethyl)-5-propoxy-1H-indole 7 (270 mg, 1.05 mmol) in 10mL of CH$_2$Cl$_2$:MeOH (1:3 v/v, 0.8 mmol/mL). After 24h, the crude was purified by flash column at 9:1 CH$_2$Cl$_2$:MeOH with NH$_3$ 1%, to afford 14p as an orange foam (25 mg, 3.69%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.26 – 8.12 (m, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.4 Hz, 1H), 7.36 (d, J = 8.5 Hz, 1H), 7.33 – 7.28 (m, 5H), 7.25 – 7.14 (m, 1H), 7.00 (d, J = 13.9 Hz, 2H), 6.81 (dd, J = 8.8, 2.3 Hz, 1H), 6.48 (1, J = 92.6 Hz, 1H), 6.09 (s, 1H), 4.04 (s, 1H), 3.94 (dd, J = 13.0, 6.4 Hz, 3H), 3.64 (dd, J = 12.0, 6.1 Hz, 2H), 3.53 – 3.48 (m, 2H), 3.37 – 3.21 (m, 2H), 2.97 (t, J = 6.2 Hz, 2H), 2.90 – 2.79 (m, 2H), 1.98 – 1.74 (m, 5H), 1.60 – 1.45 (m, 5H), 1.13 (s, 5H), 1.05 (dd, J = 14.0, 6.7 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 177.67, 167.77, 163.23, 155.66, 153.71, 145.30, 140.17, 134.72, 131.76, 129.50, 128.34, 127.86, 127.27, 126.23, 126.09, 124.41, 123.16, 120.00, 118.21, 113.08, 112.26, 112.17, 101.82, 70.56, 63.50, 53.86, 50.53, 39.49, 36.14, 35.60, 32.15, 29.84, 28.89, 25.09, 23.84, 22.96, 10.78.

HRMS ESI-TOF [M+H]$^+$ m/z calcd. for C$_{41}$H$_{49}$N$_{4}$O$_{5}$: 677.3697, found: 677.3686.
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