Supporting Information

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**Targeted Fluoro Positioning for the Discovery of a Potent and Highly Selective Matrix Metalloproteinase Inhibitor**

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Supporting Information

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General

All NMR spectra were recorded on a Bruker AVANCE III HD 500 One Bay spectrometer with a magnetic field of 11.75 T. For $^1$H NMR spectra a frequency of 500 MHz resulted. Chemical shifts are reported in ppm from tetramethylsilane as internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, br. = broad, m = multiplet), coupling constants (Hz), integration. For $^{13}$C NMR spectra a frequency of 125 MHz resulted. Chemical shifts are reported in ppm from tetramethylsilane as internal standard, whereas fluorine coupling was observed, it was reported with multiplicity (d = doublet) and coupling constants (Hz), number of carbon atoms. The multiplicities of the signals were determined by DEPT measurements. High-resolution mass spectrometry was performed on an Agilent Technologies 6530 Q-TOF. NMR and HRMS spectra as well as IC$_{50}$ curves can be found at the end of this document.
Chemistry

All reagents and solvents were purchased from Sigma Aldrich, TCI or Fluorochem and used as received. Solvents were stored over molecular sieves 4 Å.

The described compounds were synthesized according to the route described in scheme 1.

Scheme 1. Synthesis of the carboxylic acids 2a-g. a) Benzyl-bromoalkylereth, Cs₂CO₃, DMF, RT, 18 h; b) KOH 10 % in H₂O, methanol, RT, 30 min.; c) KOH, Fluorobenzylbromide, DMF, RT, 18 h; d) SOCl₂, DIPEA, THF, RT, 2h; e) Pd/C 10 %, ethanol, RT, 2h; f) TEMPO, sodiumphosphate 0.67 M in H₂O pH 6.7, NaClO₂, NaOCl, ACN, 40 °C, 4 h.
Synthesis

Methyl 2-{4-[3-(benzyloxy)propoxy]phenyl}acetate (4a; ZHAWOC4496)

Under an argon atmosphere, methyl 2-(4-hydroxyphenyl)acetate (3) (1.00 g, 6.02 mmol) and caesium carbonate (3.92 g, 12.04 mmol) were suspended in dimethylformamide (45 ml), the mixture was stirred at ambient temperature for 2 h. Benzyl-3-bromopropylether (1.52 g, 6.62 mmol) was added and it was stirred at ambient temperature for further 12 h. Water (80 ml) and ethyl acetate (80 ml) were added and the resulting phases separated. The organic phase was dried over sodium sulfate and concentrated in vacuum. Purification by chromatography on silica gel (Gradient: 0 % - 100 % ethyl acetate in cyclohexane) afforded the title compound 4a as a white solid (1.46 g, 77 % yield): \(^1\)H-NMR (500 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta = 7.35\) - 7.20 (m, 5H), 7.19 - 7.13 (m, 2H), 6.87 - 6.79 (m, 2H), 4.49 (s, 2H), 4.04 (t, J = 6.24 Hz, 2H), 3.65 (s, 3H), 3.63 (t, J = 6.15 Hz, 2H), 3.53 (s, 2H), 2.05 (quint., J = 6.20 Hz, 2H) ppm. \(^{13}\)C-NMR (125 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta = 172.39, 158.21, 138.49, 130.30, 128.43, 127.65, 127.61, 127.60, 114.69, 73.07, 66.86, 64.89, 51.99, 40.33, 29.80\) ppm. HRMS-TOF: m/z [M+H]\(^+\) calculated for C\(_{19}\)H\(_{22}\)O\(_4\): 315.1597, found: 315.1590.

In analogy to ZHAWOC4496 the following derivatives were synthesized:

Methyl 2-{4-[4-(benzyloxy)butoxy]phenyl}acetate (4b; ZHAWOC4534)

The title compound 4b was obtained as a white solid in 68 % yield: \(^1\)H-NMR (500 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta = 7.37\) - 7.22 (m, 5H), 7.20 - 7.12 (m, 2H), 6.86 - 6.79 (m, 2H), 4.50 (s, 2H), 3.95 (t, J = 6.08 Hz, 2H), 3.66 (s, 3H), 3.54 (s, 2H), 3.53 (t, J = 6.08 Hz, 2H), 1.93 - 1.72 (m, 4H) ppm. \(^{13}\)C-NMR (125 MHz, CDCl\(_3\), 25 °C, TMS): \(\delta = 172.40, 158.22, 138.59, 130.26, 128.40, 127.66, 127.57, 125.93, 114.63, 72.94, 69.95, 67.67, 51.99, 40.32, 26.40, 26.18\) ppm. HRMS-TOF: m/z [M+H]\(^+\) calculated for C\(_{20}\)H\(_{24}\)O\(_4\): 329.1754, found: 329.1744.
Methyl 2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (4c; ZHAWOC5921)

The title compound 4c was obtained as a white solid in 90 % yield: $^1$H-NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 7.43-7.30 (m, 5H), 7.26-7.21 (m, 2H), 6.93-6.88 (m, 2H), 4.56 (s, 2H), 3.99 (t, $J = 6.46$ Hz, 2H), 3.72 (s, 3H), 3.61 (s, 2H), 3.56 (t, $J = 6.46$ Hz, 2H), 1.89-1.81 (m, 2H), 1.79-1.72 (m, 2H), 1.66-1.58 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 172.22, 158.18, 138.59, 130.16, 128.28, 127.53, 127.42, 125.82, 114.51, 72.84, 70.15, 67.71, 51.82, 40.20, 29.48, 29.05, 22.77 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{21}$H$_{26}$O$_4$: 343.1910, found: 343.1903.

Methyl 2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetate (4d; ZHAWOC5946)

The title compound 4d was obtained as a white solid in 74 % yield: $^1$H-NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 7.39-7.34 (m, 4H), 7.32-7.27 (m, 1H), 7.22-7.18 (m, 2H), 6.88-6.84 (m, 2H), 4.53 (s, 2H), 3.95 (t, $J = 6.51$ Hz, 2H), 3.70 (s, 3H), 3.58 (s, 2H), 3.50 (t, $J = 6.51$ Hz, 2H), 1.84-1.76 (m, 2H), 1.71-1.64 (m, 2H), 1.53-1.43 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 172.42, 158.31, 138.73, 130.29, 128.41, 127.68, 127.55, 125.91, 114.65, 72.94, 70.37, 67.92, 52.02, 40.37, 29.78, 29.30, 26.07, 25.99 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{22}$H$_{28}$O$_4$: 357.2067, found: 357.2056.

2-{4-[3-(benzyloxy)propoxy]phenyl}acetic acid (5a; ZHAWOC4497)

The ester (4a) (0.50 g, 1.59 mmol) was dissolved in methanol (26 ml) and stirred at ambient temperature. Potassium hydroxide 10 % in water (26 ml) was added over 10 min. and the mixture was stirred for another 20 min. Methanol was removed in vacuum and the aqueous phase extracted with diethyl ether (30 ml). The aqueous phase was acidified with concentrated hydrochloric acid and extracted with diethyl
ether (50 ml). The second organic phase was dried over sodium sulfate and concentrated in vacuum to obtain the title compound 5a as a white solid (0.48 g, 98 % yield): $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 12.24 (br. s, 1H), 7.36-7.23 (m, 5H), 7.20-7.11 (m, 2H), 6.90-6.80 (m, 2H), 4.48 (s, 2H), 4.02 (t, J = 6.33 Hz, 2H), 3.59 (t, J = 6.33 Hz, 2H), 3.49 (s, 2H), 1.99 (quint., J = 6.33 Hz, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 173.43, 157.83, 139.00, 130.79, 128.66, 127.83, 127.77, 127.38, 114.67, 72.40, 66.76, 64.99, 40.29, 29.64 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{18}$H$_{20}$O$_4$: 301.1441, found: 301.1428.

In analogy to ZHAWOC4497 the following derivatives were synthesized:

2-{4-[4-(benzyloxy)butoxy]phenyl}acetic acid (5b; ZHAWOC4535)

![Image of 2-{4-[4-(benzyloxy)butoxy]phenyl}acetic acid](image)

The title compound 5b was obtained as a white solid in 90 % yield: $^1$H-NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 8.90 (br. s, 1H), 7.36-7.23 (m, 5H), 7.19-7.11 (m, 2H), 6.86-6.78 (m, 2H), 4.51 (s, 2H), 3.94 (t, J = 6.03 Hz, 2H), 3.55 (s, 2H), 3.53 (t, J = 6.03 Hz, 2H), 1.92-1.71 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 177.93, 158.34, 138.47, 130.41, 128.42, 127.73, 127.62, 125.32, 114.68, 72.93, 69.93, 67.67, 40.20, 26.35, 26.14 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{19}$H$_{22}$O$_4$: 315.1597, found: 315.1582.

2-{4-{[5-(benzyloxy)pentyl]oxy}phenyl}acetic acid (5c; ZHAWOC5922)

![Image of 2-{4-{[5-(benzyloxy)pentyl]oxy}phenyl}acetic acid](image)

The title compound 5c was obtained as a white solid in 91 % yield: $^1$H-NMR (500 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 7.36-7.26 (m, 5H), 7.20-7.16 (m, 2H), 6.88-6.83 (m, 2H), 4.53 (s, 2H), 3.94 (t, J = 6.48 Hz, 2H), 3.55 (s, 2H), 3.57 (t, J = 6.48 Hz, 2H), 1.83-1.76 (m, 2H), 1.74-1.67 (m, 2H), 1.59-1.51 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, CDCl$_3$, 25 °C, TMS): $\delta$ = 177.20, 158.31, 138.48, 130.39, 128.40, 127.71, 127.59, 125.48, 114.64, 72.90, 70.21, 67.83, 40.21, 29.47, 29.09, 22.79 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{20}$H$_{24}$O$_4$: 329.1754, found: 329.1746.
2-(4-{[6-(benzyloxy)hexyloxy]phenyl}acetic acid (5d; ZHAWOC5947)

The title compound 5d was obtained as a white solid in 73 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 12.23 (br. s, 1H), 7.36-7.23 (m, 5H), 7.18-7.12 (m, 2H), 6.87-6.81 (m, 2H), 4.44 (s, 2H), 3.91 (t, $J$ = 6.50 Hz, 2H), 3.47 (s, 2H), 3.42 (t, $J$ = 6.50 Hz, 2H), 1.73-1.65 (m, 2H), 1.59-1.52 (m, 2H), 1.45-1.33 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 173.45, 157.90, 139.20, 130.79, 128.66, 127.84, 127.75, 127.25, 114.64, 72.27, 70.01, 67.77, 40.26, 29.63, 29.14, 25.96, 25.85 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C21H26O4: 343.1910, found: 343.1912.

Potassium hydroxide (1.04 g, 18.51 mmol) was added to a solution of 4-aminophthalimide (3.00 g, 18.51 mmol) in dimethylformamide (60 ml) and the mixture was stirred at ambient temperature for 2 h. 4-Fluorobenzylbromide (3.50 g, 18.51 mmol) was added and it was stirred for another 18 h at the same temperature. Water (100 ml) and ethyl acetate (100 ml) was added and the resulting phases separated. The organic phase was washed with brine, dried over sodium sulfate and concentrated in vacuum. Purification by chromatography on silica gel (Gradient: 0 % - 100 % ethyl acetate in cyclohexane) afforded the title compound 7b as a yellow solid (3.40 g, 68 % yield): $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 7.49 (d, $J$ = 8.14 Hz, 1H), 7.33-7.28 (m, 2H), 7.17-7.11 (m, 2H), 6.93 (d, $J$ = 1.94 Hz, 1H), 6.80 (dd, $J$ = 8.14 Hz, 1.94 Hz, 1H), 6.50 (s, 2H), 4.65 (s, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 168.50, 168.11, 161.82 (d, $J$ = 243.45 Hz, 1C), 155.55, 134.88, 133.90 (d, $J$ = 3.02 Hz, 1C), 129.95 (d, $J$ = 1.94 Hz, 1C), 125.52, 117.14, 116.87, 115.76 (d, $J$ = 21.43 Hz, 2C), 107.58, 40.22 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C15H11FN2O2: 271.0884, found: 271.0875.

Potassium hydroxide (1.04 g, 18.51 mmol) was added to a solution of 4-aminophthalimide 6 (3.00 g, 18.51 mmol) in dimethylformamide (60 ml) and the mixture was stirred at ambient temperature for 2 h. 4-Fluorobenzylbromide (3.50 g, 18.51 mmol) was added and it was stirred for another 18 h at the same temperature. Water (100 ml) and ethyl acetate (100 ml) was added and the resulting phases separated. The organic phase was washed with brine, dried over sodium sulfate and concentrated in vacuum. Purification by chromatography on silica gel (Gradient: 0 % - 100 % ethyl acetate in cyclohexane) afforded the title compound 7b as a yellow solid (3.40 g, 68 % yield): $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 7.49 (d, $J$ = 8.14 Hz, 1H), 7.33-7.28 (m, 2H), 7.17-7.11 (m, 2H), 6.93 (d, $J$ = 1.94 Hz, 1H), 6.80 (dd, $J$ = 8.14 Hz, 1.94 Hz, 1H), 6.50 (s, 2H), 4.65 (s, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 168.50, 168.11, 161.82 (d, $J$ = 243.45 Hz, 1C), 155.55, 134.88, 133.90 (d, $J$ = 3.02 Hz, 1C), 129.95 (d, $J$ = 1.94 Hz, 1C), 125.52, 117.14, 116.87, 115.76 (d, $J$ = 21.43 Hz, 2C), 107.58, 40.22 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C15H11FN2O2: 271.0884, found: 271.0875.

In analogy to ZHAWOC3199 the following derivatives were synthesized:
5-amino-2-[[3-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione  
(7c; ZHAWOC6017)

The title compound 7c was obtained as a yellow solid in 42 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 7.51$ (d, J = 8.22 Hz, 1H), 7.39-7.33 (m, 1H), 7.11-7.06 (m, 3H), 6.95 (d, J = 2.05 Hz, 1H), 6.81 (dd, J = 8.22 Hz, 2.05 Hz, 1H), 6.51 (s, 2H), 4.69 (s, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 168.51$, 168.10, 162.61 (d, J = 242.50 Hz, 1C), 155.59, 140.51 (d, J = 7.50 Hz, 1C), 134.88, 131.06 (d, J = 7.50 Hz, 1C), 125.59, 123.66 (d, J = 2.50 Hz, 1C), 117.17, 116.83, 114.59 (d, J = 21.25 Hz, 1C), 114.54 (d, J = 22.50 Hz, 1C), 107.61, 40.43 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{15}$H$_{11}$FN$_2$O$_2$: 271.0884, found: 271.0868.

5-amino-2-[[2-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione  
(7d; ZHAWOC1246)

The title compound 7d was obtained as a yellow solid in 42 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 7.50$ (d, J = 8.22 Hz, 1H), 7.35-7.29 (m, 1H), 7.25-7.11 (m, 3H), 6.94 (d, J = 1.95 Hz, 1H), 6.81 (dd, J = 8.22 Hz, 1.95 Hz, 1H), 6.50 (s, 2H), 4.73 (s, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 168.38$, 167.95, 160.23 (d, J = 243.75 Hz, 1C), 155.58, 134.85, 129.88 (d, J = 5.00 Hz, 1C), 129.83, 125.56, 125.00 (d, J = 3.75 Hz, 1C), 124.27 (d, J = 13.75 Hz, 1C), 117.18, 116.86, 115.80 (d, J = 21.25 Hz, 1C), 107.57, 34.92 (d, J = 5.00 Hz, 1C) ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{15}$H$_{11}$FN$_2$O$_2$: 271.0884, found: 271.0875.

N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-{4-[3-(benzyloxy)propoxy]phenyl}acetamide (8a; ZHAWOC4511)
The acid (5a) (4.50 g, 14.99 mmol) was stirred in an excess of thionyl chloride at 55 °C for 1 h. After removal of excess thionyl chloride in vacuum, the acid chloride was dissolved in tetrahydrofuran (20 ml) and added to a solution of 5-amino-2-benzylisindoline-1,3-dione (7a) (1.9 g, 7.50 mmol) in tetrahydrofuran (200 ml) under argon at ambient temperature. Diisopropylethylamine (2.28 g, 17.65 mmol) was added and the mixture was stirred at ambient temperature for 2 h. After removal of the tetrahydrofuran in vacuum, ethyl acetate (250 ml) and 10 % citric acid (250 ml) were added and the resulting phases were separated. The organic phase was washed with 10 % sodium bicarbonate (250 ml) and brine (250 ml), dried over sodium sulfate and concentrated in vacuum. Purification by chromatography on silica gel (Gradient: 0 % - 100 % ethyl acetate in cyclohexane) afforded the title compound 8a as a yellow solid (2.50 g, 62 % yield): ¹H-NMR (500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 10.73 (s, 1H), 8.21 (d, J = 1.80 Hz, 1H), 7.89 (dd, J = 8.31 Hz, 1.80 Hz, 1H), 7.80 (d, J = 8.31 Hz, 1H), 7.35-7.21 (m, 12H), 6.91-6.85 (m, 2H), 4.73 (s, 2H), 4.47 (s, 2H), 4.02 (t, J = 6.35 Hz, 2H), 3.64 (s, 2H), 3.57 (t, J = 6.35 Hz, 2H), 1.97 (quint., J = 3.65 Hz, 2H) ppm. ¹³C-NMR (125 MHz, [D₆]DMSO, 25 °C, TMS): δ = 170.92, 167.93, 167.76, 157.93, 145.30, 139.00, 137.21, 133.54, 130.66, 129.04, 128.67, 127.84, 127.83, 127.63, 127.56, 125.73, 124.94, 123.83, 114.84, 113.34, 72.35, 66.72, 65.02, 42.96, 41.31, 29.61 ppm. HRMS-TOF: m/z [M+H]⁺ calculated for C₃₃H₃₀N₂O₅: 535.2234, found: 535.2223.

In analogy to ZHAW4511 the following derivatives were synthesized:

N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-[4-[4-(benzyloxy)butoxy]phenyl]acetamide (8b; ZHAWOC4752)

The title compound 8b was obtained as a yellow solid in 64 % yield: ¹H-NMR (500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 10.73 (s, 1H), 8.21 (d, J = 1.83 Hz, 1H), 7.89 (dd, J = 8.23 Hz, 1.83 Hz, 1H), 7.84 (d, J = 8.23 Hz, 1H), 7.35-7.21 (m, 12H), 6.89-6.85 (m, 2H), 4.73 (s, 2H), 4.45 (s, 2H), 3.95 (t, J = 6.27 Hz, 2H), 3.63 (s, 2H), 3.48 (t, J = 6.27 Hz, 2H), 1.79-1.72 (m, 2H), 1.72-1.64 (m, 2H) ppm. ¹³C-NMR (125 MHz, [D₆]DMSO, 25 °C, TMS): δ = 170.95, 167.96, 167.78, 157.99, 145.32, 139.14, 137.23, 133.55, 130.65, 129.06, 128.69, 127.89, 127.87, 127.84, 127.78, 127.56, 125.73, 124.94, 123.83, 114.84, 113.34, 72.28, 69.75, 67.66, 42.97, 41.32, 26.29, 26.10 ppm. HRMS-TOF: m/z [M+H]⁺ calculated for C₃₄H₃₂N₂O₅: 549.2390, found: 549.2380.
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetamide (8c; ZHAWOC5979)

The title compound 8c was obtained as a white solid in 44 % yield: 

$^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.73 (s, 1H), 8.21 (d, $J = 1.83$ Hz, 1H), 7.89 (dd, $J = 8.23$ Hz, 1H), 7.84 (d, $J = 8.23$ Hz, 1H), 7.35-7.21 (m, 12H), 6.89-6.85 (m, 2H), 4.73 (s, 2H), 4.44 (s, 2H), 3.93 (t, $J = 6.47$ Hz, 2H), 3.63 (s, 2H), 3.43 (t, $J = 6.39$ Hz, 2H), 1.74-1.66 (m, 2H), 1.63-1.56 (m, 2H), 1.50-1.42 (m, 2H) ppm. 

$^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.93, 167.94, 167.76, 158.01, 145.30, 139.17, 137.21, 133.54, 130.63, 129.05, 128.67, 127.85, 127.83, 127.76, 127.51, 125.72, 124.93, 123.81, 114.82, 113.33, 72.27, 69.97, 67.79, 42.96, 41.31, 29.38, 28.95, 22.84 ppm. 

HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{35}$H$_{34}$N$_2$O$_5$: 563.2547, found: 563.2557.

2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)-N-[2-[[4-fluorophenyl]methyl]-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl]acetamide (8d; ZHAWOC5682)

The title compound 8d was obtained as a yellow solid in 58 % yield: 

$^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.72 (s, 1H), 8.20 (d, $J = 1.82$ Hz, 1H), 7.88 (dd, $J = 8.27$ Hz, 1.82 Hz, 1H), 7.83 (d, $J = 8.27$ Hz, 1H), 7.36-7.21 (m, 9H), 7.17-7.11 (m, 2H), 6.90-6.85 (m, 2H), 4.72 (s, 2H), 4.44 (s, 2H), 3.92 (t, $J = 6.45$ Hz, 2H), 3.63 (s, 2H), 3.43 (t, $J = 6.40$ Hz, 2H), 1.73-1.66 (m, 2H), 1.62-1.55 (m, 2H), 1.50-1.42 (m, 2H) ppm. 

$^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.92, 167.89, 167.71, 161.90 (d, $J = 243.23$ Hz, 1C), 158.01, 145.30, 139.17, 133.54, 133.45 (d, $J = 3.06$ Hz, 1C), 130.63, 130.08 (d, $J = 8.28$ Hz, 2C), 128.66, 127.84, 127.75, 127.50, 125.71, 124.92, 123.80, 115.81 (d, $J = 21.43$ Hz, 2C), 114.81, 113.33, 72.27, 69.97, 67.79, 42.96, 40.62, 29.38, 28.95, 22.84 ppm. 

HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{35}$H$_{33}$FN$_2$O$_5$: 581.2453, found: 581.2444.
2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)-N-[2-[[3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]acetamide (8e; ZHAWOC6018)

The title compound 8e was obtained as a white solid in 34 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.73 (s, 1H), 8.21 (d, J = 1.86 Hz, 1H), 7.89 (dd, J = 8.21 Hz, 1.86 Hz, 1H), 7.84 (d, J = 8.21 Hz, 1H), 7.39-7.21 (m, 8H), 7.15-7.07 (m, 3H), 6.90-6.86 (m, 2H), 4.75 (s, 2H), 4.44 (s, 2H), 3.93 (t, J = 6.45 Hz, 2H), 3.63 (s, 2H), 3.43 (t, J = 6.35 Hz, 2H), 1.74-1.66 (m, 2H), 1.63-1.56 (m, 2H), 1.50-1.42 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.92, 167.73, 162.64 (d, J = 242.5 Hz, 1C), 158.02, 145.30, 140.03 (d, J = 6.25 Hz, 1C), 139.17, 133.58, 131.07 (d, J = 8.75 Hz, 1C), 130.63, 128.67, 127.85, 127.75, 127.51, 125.75, 124.96, 123.81, 123.75 (d, J = 3.75 Hz, 1C), 114.82, 114.69 (d, J = 20 Hz, 1C), 114.64 (d, J = 22.5 Hz, 1C), 113.36, 72.27, 69.97, 67.79, 42.96, 40.82, 29.38, 28.95, 22.84 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{35}$H$_{33}$FN$_2$O$_5$: 581.2453, found: 581.2444.

2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)-N-[2-[[2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]acetamide (8f; ZHAWOC6019)

The title compound 8f was obtained as a white solid in 31 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.73 (s, 1H), 8.21 (d, J = 1.75 Hz, 1H), 7.90 (dd, J = 8.23 Hz, 1.75 Hz, 1H), 7.84 (d, J = 8.23 Hz, 1H), 7.35-7.11 (m, 11H), 6.90-6.85 (m, 2H), 4.78 (s, 2H), 4.43 (s, 2H), 3.93 (t, J = 6.45 Hz, 2H), 3.63 (s, 2H), 3.43 (t, J = 6.38 Hz, 2H), 1.73-1.66 (m, 2H), 1.62-1.55 (m, 2H), 1.50-1.42 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.75, 167.54, 160.31 (d, J = 243.75 Hz, 1C), 158.02, 145.32, 139.17, 133.52, 130.63, 130.12 (d, J = 3.75 Hz, 1C), 130.05 (d, J = 8.75 Hz, 1C), 128.67, 127.85, 127.75, 127.50, 125.70, 125.01 (d, J = 2.5 Hz, 1C), 124.95, 123.84, 123.81 (d, J = 13.75 Hz, 1C), 115.83 (d, J = 21.25 Hz, 1C), 114.81, 113.33, 72.27, 69.97, 67.79, 42.96, 35.40 (d, J = 3.75 Hz, 1C), 29.38, 28.95, 22.84 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{35}$H$_{33}$FN$_2$O$_5$: 581.2453, found: 581.2431.
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-(4-[(6-(benzyloxy)hexyloxy)phenyl)]acetamide (8g; ZHAWOC5980)

The title compound 8g was obtained as a white solid in 34% yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.73 (s, 1H), 8.21 (d, J = 1.83 Hz, 1H), 7.89 (dd, J = 8.23 Hz, 1.83 Hz, 1H), 7.83 (d, J = 8.23 Hz, 1H), 7.34-7.21 (m, 12H), 6.89-6.85 (m, 2H), 4.73 (s, 2H), 4.43 (s, 2H), 3.91 (t, J = 6.43 Hz, 2H), 3.63 (s, 2H), 3.41 (t, J = 6.43 Hz, 2H), 1.72-1.64 (m, 2H), 1.58-1.51 (m, 2H), 1.44-1.32 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 170.93, 167.93, 167.75, 158.03, 145.31, 139.18, 137.21, 133.53, 130.63, 129.04, 128.65, 127.85, 127.84, 127.74, 127.50, 125.71, 124.91, 123.80, 114.80, 113.32, 72.25, 69.99, 67.79, 42.97, 41.31, 29.62, 29.11, 25.95, 25.83 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{36}$H$_{36}$N$_2$O$_5$: 577.2703, found: 577.2684.

N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-(3-hydroxypropoxy)phenyl]acetamide (9a; ZHAWOC4512)

The benzyl ether (8a) (1.10 g, 2.06 mmol) was dissolved in ethanol (100 ml). Palladium 10% on activated charcoal (0.25 g, 0.21 mmol) was added and a hydrogen atmosphere was applied at 1 bar. After stirring at ambient temperature for 2 h the mixture was filtered over celite and concentrated in vacuum. Purification by chromatography on silica gel (Gradient: 0 % - 100 % ethyl acetate in cyclohexane) afforded the title compound 9a as a white solid (0.65 g, 71% yield): $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.74 (s, 1H), 8.21 (d, J = 1.81 Hz, 1H), 7.89 (dd, J = 8.25 Hz, 1.81 Hz, 1H), 7.84 (d, J = 8.25 Hz, 1H), 7.35-7.21 (m, 7H), 6.91-6.86 (m, 2H), 4.73 (s, 2H), 4.52 (t, J = 4.60 Hz, 1H), 4.00 (t, J = 6.42 Hz, 2H), 3.64 (s, 2H), 3.54 (m, 2H), 1.84 (quint., J = 6.31 Hz, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 170.93, 167.94, 167.76, 158.03, 145.30, 137.21, 130.64, 129.04, 127.86, 127.83, 127.51, 125.72, 124.92, 123.81, 114.80, 113.32, 64.99, 57.77, 42.95, 41.31, 32.60 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{26}$H$_{24}$N$_2$O$_5$: 445.1764, found: 445.1759.

In analogy to ZHAW4512 the following derivatives were synthesized:
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-[4-(4-hydroxybutoxy)phenyl]acetamide (9b; ZHAWOC4753)

The title compound 9b was obtained as a white solid in 60% yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.74 (s, 1H), 8.21 (d, J = 1.83 Hz, 1H), 7.90 (dd, J = 8.24 Hz, 1.83 Hz, 1H), 7.84 (d, J = 8.24 Hz, 1H), 7.35-7.22 (m, 7H), 6.91-6.86 (m, 2H), 4.74 (s, 2H), 4.44 (t, J = 4.54 Hz, 1H), 4.95 (t, J = 6.44 Hz, 2H), 3.64 (s, 2H), 3.44 (m, 2H), 1.76-1.69 (m, 2H), 1.59-1.51 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.94, 167.76, 158.02, 145.32, 137.21, 133.54, 130.54, 129.04, 127.86, 127.83, 127.50, 125.71, 124.92, 123.81, 114.81, 113.33, 67.82, 60.86, 42.96, 41.31, 29.47, 25.91 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{27}$H$_{26}$N$_2$O$_5$: 459.1921, found: 459.1899.

N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-[4-[(5-hydroxypentyl)oxy]phenyl]acetamide (9c; ZHAWOC5130)

The title compound 9c was obtained as a white solid in 24% yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.72 (s, 1H), 8.21 (d, J = 1.84 Hz, 1H), 7.89 (dd, J = 8.26 Hz, 1.84 Hz, 1H), 7.84 (d, J = 8.26 Hz, 1H), 7.35-7.25 (m, 5H), 7.25-7.21 (m, 2H), 6.90-6.85 (m, 2H), 4.73 (s, 2H), 4.36 (t, J = 5.16 Hz, 1H), 3.93 (t, J = 6.50 Hz, 2H), 3.63 (s, 2H), 3.40 (td, J = 6.20 Hz, 5.16 Hz, 2H), 1.73-1.66 (m, 2H), 1.50-1.38 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.94, 167.77, 158.04, 145.30, 137.21, 133.54, 130.64, 129.05, 127.86, 127.83, 127.49, 125.72, 124.93, 123.81, 114.81, 113.33, 67.89, 61.07, 42.96, 41.32, 32.68, 29.06, 22.61 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{28}$N$_2$O$_5$: 473.2077, found: 473.2045.
N-{2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9d; ZHAWOC5683)

The title compound 9d was obtained as a white solid in 44% yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.73 (s, 1H), 8.20 (d, $J$ = 1.84 Hz, 1H), 7.89 (dd, $J$ = 8.20 Hz, 1.84 Hz, 1H), 7.83 (d, $J$ = 8.20 Hz, 1H), 7.37-7.32 (m, 2H), 7.25-7.21 (m, 2H), 7.17-7.11 (m, 2H), 6.90-6.86 (m, 2H), 4.72 (s, 2H), 4.36 (t, $J$ = 5.10 Hz, 1H), 3.93 (t, $J$ = 6.45 Hz, 2H), 3.63 (s, 2H), 3.42-3.38 (m, 2H), 1.73-1.65 (m, 2H), 1.50-1.37 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.90, 167.72, 161.90 (d, $J$ = 242.58 Hz, 1C), 158.04, 145.30, 133.55, 133.44 (d, $J$ = 3.08 Hz, 1C), 130.64, 130.07 (d, $J$ = 8.33 Hz, 2C), 127.49, 125.72, 124.93, 123.81, 115.82 (d, $J$ = 21.42 Hz, 2C), 114.80, 113.36, 67.88, 61.07, 42.95, 40.62, 32.68, 29.05, 22.61 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{27}$FN$_2$O$_5$: 491.1983, found: 491.1968.

N-{2-[(3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9e; ZHAWOC6021)

The title compound 9e was obtained as a white solid in 46% yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 10.73 (s, 1H), 8.21 (d, $J$ = 1.74 Hz, 1H), 7.89 (dd, $J$ = 8.26 Hz, 1.74 Hz, 1H), 7.84 (d, $J$ = 8.26 Hz, 1H), 7.37 (td, $J$ = 7.98 Hz, 6.08 Hz, 1H), 7.26-7.21 (m, 2H), 7.16-7.07 (m, 3H), 6.90-6.86 (m, 2H), 4.75 (s, 2H), 4.36 (t, $J$ = 5.19 Hz, 1H), 3.93 (t, $J$ = 6.49 Hz, 2H), 3.64 (s, 2H), 3.42-3.38 (m, 2H), 1.73-1.65 (m, 2H), 1.50-1.37 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta$ = 170.94, 167.92, 167.73, 162.64 (d, $J$ = 242.50 Hz, 1C), 158.04, 145.30, 140.02 (d, $J$ = 7.5 Hz, 1C), 133.59, 131.07 (d, $J$ = 8.75 Hz, 1C), 130.64, 127.49, 125.76, 124.96, 123.81, 123.74 (d, $J$ = 2.5 Hz, 1C), 114.81, 114.69 (d, $J$ = 20 Hz, 1C), 114.64 (d, $J$ = 22.5 Hz, 1C), 113.36, 67.89, 61.07, 42.96, 40.82 (d, $J$ = 1.25 Hz, 1C), 32.68, 29.06, 22.61 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{27}$FN$_2$O$_5$: 491.1983, found: 491.1964.
N-{2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl}-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9f; ZHAWOC6022)

The title compound 9f was obtained as a white solid in 32 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.73 (s, 1H), 8.20 (d, J = 1.86 Hz, 1H), 7.90 (dd, J = 8.26 Hz, 1.86 Hz, 1H), 7.84 (d, J = 8.26 Hz, 1H), 7.36-7.27 (m, 2H), 7.25-7.22 (m, 2H), 7.21-7.11 (m, 2H), 6.90-6.86 (m, 2H), 4.79 (s, 2H), 4.37 (t, J = 5.17 Hz, 1H), 3.93 (t, J = 6.47 Hz, 2H), 3.63 (s, 2H), 3.40 (m, 2H), 1.73-1.65 (m, 2H), 1.50-1.37 (m, 4H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 170.95, 167.75, 167.55, 160.31 (d, J = 243.75 Hz, 1C), 158.04, 145.32, 133.52, 130.64, 130.12 (d, J = 3.75 Hz, 1C), 130.05 (d, J = 8.75 Hz, 1C), 127.49, 125.71, 125.02 (d, J = 3.75 Hz, 1C), 124.96, 123.85, 123.81 (d, J = 13.75 Hz, 1C), 115.83 (d, J = 21.25 Hz, 1C), 114.81, 113.33, 67.89, 61.07, 42.95, 35.40 (d, J = 5 Hz, 1C), 32.68, 29.05, 22.60 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{27}$FN$_2$O$_5$: 491.1983, found: 491.1975.

N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-{4-[(6-hydroxyhexyl)oxy]phenyl}acetamide (9g; ZHAWOC5132)

The title compound 9g was obtained as a white solid in 6 % yield: $^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 10.73 (s, 1H), 8.21 (d, J = 1.82 Hz, 1H), 7.89 (dd, J = 8.23 Hz, 1.82 Hz, 1H), 7.84 (d, J = 8.23 Hz, 1H), 7.35-7.25 (m, 5H), 7.25-7.21 (m, 2H), 6.90-6.85 (m, 2H), 4.74 (s, 2H), 4.33 (t, J = 5.16 Hz, 1H), 3.92 (t, J = 6.50 Hz, 2H), 3.63 (s, 2H), 3.38 (td, J = 6.32 Hz, 5.16 Hz, 2H), 1.72-1.65 (m, 2H), 1.47-1.29 (m, 6H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 170.94, 167.94, 167.77, 158.03, 145.30, 137.21, 133.54, 130.64, 129.05, 127.86, 127.83, 127.49, 125.72, 124.93, 123.81, 114.81, 113.33, 67.82, 61.10, 42.95, 41.32, 32.95, 29.22, 25.90, 25.74 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{29}$H$_{30}$N$_2$O$_5$: 487.2234, found: 487.2210.
3-(4-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]propanoic acid (2a; ZHAWOC4765)

The alcohol (9a) (0.26 g, 0.59 mmol), TEMPO (0.06 g, 0.38 mmol) and 0.67 M aqueous sodium phosphate (2.6 ml) in acetonitrile (3.2 ml) were stirred and heated to 40 °C. NaClO₂ (0.13 g, 1.17 mmol in 0.60 ml water) and 0.25 % NaOCl (0.26 ml) were added in parallel dropwise and it was stirred for 4 h. After cooling to ambient temperature, water (2 ml) was added and the mixture was poured in an ice cold solution of Na₂SO₃ (0.12 g in 2 ml water). The aqueous phase was extracted with diethyl ether (10 ml), acidified with 10 % citric acid and again extracted with diethyl ether (2 x 10 ml). The organic phases were dried over sodium sulfate and concentrated in vacuum to obtain the title compound 2a as a white solid (0.23 g, 86 % yield, purity 98 %): ¹H-NMR (500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 11.94 (br. s, 1H), 10.77 (s, 1H), 8.21 (d, J = 1.75 Hz, 1H), 7.90 (dd, J = 8.22 Hz, 1.75 Hz, 1H), 7.83 (d, J = 8.22 Hz, 1H), 7.35-7.22 (m, 7H), 6.91-6.87 (m, 2H), 4.73 (s, 2H), 4.14 (t, J = 6.02 Hz, 2H), 3.64 (s, 2H), 2.67 (t, J = 6.02 Hz, 2H) ppm. ¹³C-NMR (125 MHz, [D₆]DMSO, 25 °C, TMS): δ = 172.81, 171.71, 17.91, 167.94, 167.77, 157.70, 145.32, 137.21, 133.53, 130.69, 129.04, 127.85, 127.82, 125.71, 124.91, 123.82, 114.80, 113.34, 64.08, 42.93, 41.31, 34.67 ppm. HRMS-TOF: m/z [M+H]+ calculated for C₂₆H₂₂N₂O₅: 459.1557, found: 459.1538.

In analogy to ZHAW4765 the following derivatives were synthesized:

4-(4-[[[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl]methyl]phenoxy]butanoic acid (2b; ZHAWOC4766)

The title compound 2b was obtained as a white solid in 67 % yield and 95 % purity: ¹H-NMR (500 MHz, [D₆]DMSO, 25 °C, TMS): δ = 12.14 (br. s, 1H), 10.73 (s, 1H), 8.21 (d, J = 1.80 Hz, 1H), 7.89 (dd, J = 8.21 Hz, 1.80 Hz, 1H), 7.84 (d, J = 8.21 Hz, 1H), 7.34-7.21 (m, 7H), 6.90-6.86 (m, 2H), 4.73 (s, 2H), 3.95 (t, J = 6.41 Hz, 2H), 3.64 (s, 2H), 2.36 (t, J = 6.41 Hz, 2H), 1.92 (quint., J = 6.75 Hz, 2H) ppm. ¹³C-NMR (125 MHz, [D₆]DMSO, 25 °C, TMS): δ = 174.55, 170.92, 167.94, 167.77, 157.86, 145.30, 137.21, 133.54, 130.66, 129.05, 127.86, 127.83, 127.66, 125.72, 124.93,
123.82, 114.84, 113.33, 67.02, 42.94, 41.31, 30.61, 24.72 ppm. HRMS-TOF: m/z [M+H]^+ calculated for C27H24N2O6: 473.1713, found: 473.1699.

5-4-[[2-(benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)carbamoyl]methyl]phenoxy]pentanoic acid (2c; ZHAWOC5131)

The title compound 2c was obtained as a white solid in 62 % yield and 99 % purity:

^1^H-NMR (500 MHz, [D_6]DMSO, 25 °C, TMS): δ = 10.75 (s, 1H), 8.21 (d, J = 1.83 Hz, 1H), 7.89 (dd, J = 8.25 Hz, 1.83 Hz, 1H), 7.83 (d, J = 8.25 Hz, 1H), 7.34-7.21 (m, 7H), 6.90-6.86 (m, 2H), 4.73 (s, 2H), 3.93 (t, J = 6.18 Hz, 2H), 3.63 (s, 2H), 2.27 (t, J = 7.35 Hz, 2H), 1.74-1.67 (m, 2H), 1.66-1.59 (m, 2H) ppm. ^13^C-NMR (125 MHz, [D_6]DMSO, 25 °C, TMS): δ = 174.85, 170.93, 167.94, 167.76, 157.97, 145.31, 137.21, 133.53, 130.64, 129.04, 127.85, 127.82, 127.55, 125.71, 124.91, 123.81, 114.81, 113.33, 67.55, 42.95, 41.31, 33.81, 28.60, 21.71 ppm. HRMS-TOF: m/z [M+H]^+ calculated for C28H26N2O6: 487.1870, found: 487.1853.

5-4-[[2-[[4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl)methyl]phenoxy]pentanoic acid (2d; ZHAWOC5684)

The title compound 2d was obtained as a white solid in 50 % yield and 96 % purity:

^1^H-NMR (500 MHz, [D_6]DMSO, 25 °C, TMS): δ = 11.92 (br. s, 1H), 10.74 (s, 1H), 8.20 (d, J = 1.82 Hz, 1H), 7.89 (dd, J = 8.25 Hz, 1.82 Hz, 1H), 7.83 (d, J = 8.25 Hz, 1H), 7.37-7.31 (m, 2H), 7.26-7.21 (m, 2H), 7.17-7.11 (m, 2H), 6.90-6.86 (m, 2H), 4.72 (s, 2H), 3.94 (t, J = 6.16 Hz, 2H), 3.63 (s, 2H), 2.27 (t, J = 6.41 Hz, 2H), 1.75-1.67 (m, 2H), 1.66-1.59 (m, 2H) ppm. ^13^C-NMR (125 MHz, [D_6]DMSO, 25 °C, TMS): δ = 174.83, 170.93, 167.90, 167.72, 161.90 (d, J = 243.25 Hz, 1C), 157.97, 145.30, 133.54, 133.44 (d, J = 3.03 Hz, 1C), 130.64, 130.07 (d, J = 8.24 Hz, 2C), 127.55, 125.71, 124.93, 123.81, 115.81 (d, J = 21.45 Hz, 2C), 114.81, 113.33, 67.54, 42.95, 40.63, 33.76, 28.59, 21.69 ppm. HRMS-TOF: m/z [M+H]^+ calculated for C28H25FN2O6: 505.1776, found: 505.1758.
5-{4-[[2-[[3-fluorophenyl]methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl]methyl]phenoxy}pentanoic acid (2e; ZHAWOC6023)

The title compound 2e was obtained as a white solid in 47 % yield and 97 % purity: 
$^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 12.12$ (br. s, 1H), 10.83 (s, 1H), 8.30 (d, $J = 1.82$ Hz, 1H), 7.98 (dd, $J = 8.27$ Hz, 1.82 Hz, 1H), 7.93 (d, $J = 8.27$ Hz, 1H), 7.46 (td, $J = 8.08$ Hz, 6.06 Hz, 1H), 7.35-7.31 (m, 2H), 7.25-7.16 (m, 3H), 6.99-6.95 (m, 2H), 4.84 (s, 2H), 4.03 (t, $J = 6.17$ Hz, 2H), 3.73 (s, 2H), 2.36 (t, $J = 7.43$ Hz, 2H), 1.83-1.76 (m, 2H), 1.76-1.68 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 174.83, 170.93, 167.92, 167.74, 162.64$ (d, $J = 242.50$ Hz, 1C), 157.97, 145.30, 140.03 (d, $J = 7.5$ Hz, 1C), 133.59, 131.07 (d, $J = 7.5$ Hz, 1C), 130.64, 127.56, 125.76, 124.96, 123.78 (d, $J = 7.5$ Hz, 1C), 123.73, 114.82, 114.69 (d, $J = 20$ Hz, 1C), 114.64 (d, $J = 11$ Hz, 1C), 113.37, 67.55, 42.96, 40.82 (d; $J = 1.25$ Hz, 1C), 33.78, 28.59, 21.70 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{25}$F$_2$N$_2$O$_6$: 505.1776, found: 505.1768.

5-{4-[[2-[[2-fluorophenyl]methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl]methyl]phenoxy}pentanoic acid (2f; ZHAWOC6024)

The title compound 2f was obtained as a white solid in 33 % yield and 97 % purity: 
$^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 12.03$ (br. s, 1H), 10.73 (s, 1H), 8.21 (d, $J = 1.85$ Hz, 1H), 7.90 (dd, $J = 8.26$ Hz, 1.85 Hz, 1H), 7.84 (d, $J = 8.26$ Hz, 1H), 7.36-7.28 (m, 2H), 7.26-7.22 (m, 2H), 7.22-7.12 (m, 2H), 6.91-6.86 (m, 2H), 4.79 (s, 2H), 3.94 (t, $J = 6.19$ Hz, 2H), 3.64 (s, 2H), 2.27 (t, $J = 7.41$ Hz, 2H), 1.75-1.67 (m, 2H), 1.67-1.59 (m, 2H) ppm. $^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): $\delta = 174.83, 170.94, 167.75, 167.55, 160.31$ (d, $J = 243.75$ Hz, 1C), 157.97, 145.32, 133.52, 130.64, 130.11 (d, $J = 5$ Hz, 1C), 130.04 (d, $J = 7.5$ Hz, 1C), 127.55, 125.71, 125.03, 124.98 (d, $J = 5$ Hz, 1C), 123.85, 123.81 (d, $J = 15$ Hz, 1C), 115.83 (d, $J = 28.75$ Hz, 1C), 114.82, 113.33, 67.55, 42.95, 35.40 (d; $J = 5$ Hz, 1C), 33.78, 28.59, 21.70 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{28}$H$_{25}$FN$_2$O$_6$: 505.1776, found: 505.1763.
6-(4-[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl[methyl]phenoxy]hexanoic acid (2g; ZHAWOC5133)

The title compound 2g was obtained as a white solid in 96 % yield and 94 % purity: 

$^1$H-NMR (500 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 12.01 (br. s, 1H), 10.76 (s, 1H), 8.22 (d, J = 1.80 Hz, 1H), 7.90 (dd, J = 8.27 Hz, 1.80 Hz, 1H), 7.84 (d, J = 8.27 Hz, 1H), 7.36-7.21 (m, 7H), 6.90-6.86 (m, 2H), 4.74 (s, 2H), 3.93 (t, J = 6.48 Hz, 2H), 3.64 (s, 2H), 2.20 (t, J = 7.26 Hz, 2H), 1.73-1.66 (m, 2H), 1.59-1.51 (m, 2H); 1.44-1.37 (m, 2H) ppm. 

$^{13}$C-NMR (125 MHz, [D$_6$]DMSO, 25 °C, TMS): δ = 177.22, 171.23, 168.02, 167.83, 158.00, 145.74, 137.25, 135.44, 130.63, 129.04, 127.83, 127.79, 17.77, 125.45, 124.77, 123.96, 114.67, 113.47, 67.99, 42.86, 41.27, 38.78, 29.35, 26.76, 26.37 ppm. HRMS-TOF: m/z [M+H]$^+$ calculated for C$_{29}$H$_{28}$N$_2$O$_6$: 501.2026, found: 501.2027.

**In silico Studies**

Molecular modeling experiments were performed using the Molecular Operating Environment MOE 2015.10 from Chemical Computing Group (www.chemcomp.com). The co-crystal structure 2OW9 was selected for this work and could be obtained from the Protein Data Bank (www.rcsb.org). Using the sequence editor in MOE the duplicates could be eliminated. The pocket was prepared for the docking studies via the Protonate 3D method applying the default values for temperature 300 K, pH 7 and salt 0.1. The ligands to be docked were imported from structural data files (SD files) to receive a MOE compatible molecular database. 3D coordinates for the ligands were generated directly in MOE using rebuild3D with a root mean square deviation (RMSD) gradient of 0.1. The Amber10:EHT force field was applied for the docking experiments.

For the ortho fluorinated compound no additional interaction could be found.
**In vitro Assays**

IC<sub>50</sub> values were determined at Reaction Biology Corporation, Malvern, PA, USA in triplicates using 10 concentrations starting at 10 μM with 3 fold dilution. The substrate used for the determinations was the (5-FAM/QXL<sub>TM</sub>) FRET peptide. The buffer consisted of 50 mM HEPES at pH 7.5 with 10 mM CaCl<sub>2</sub> and 0.01 % Brij-35. 0.1 mg/ml BSA was added before use. As a control inhibitor GM6001 was used.

Solubility was determined at Bienta Enamine, Kiev, Ukraine using a 10 mM stock solution in 100 % DMSO, dilutions were prepared to a theoretical concentration of 200 μM in duplicates in phosphate-buffered saline pH 7.4 with 2 % final DMSO. In parallel, compound dilutions in 50 % acetonitrile/PBS mixes were prepared to theoretical concentrations of 0 μM (Blank), 25 μM, 100 μM and 200 μM in duplicates to generate calibration curves. The experimental compound dilutions in PBS were further allowed to equilibrate at 25 °C before centrifugation. The supernatants of test compounds were diluted 2-fold with acetonitrile before measuring. As a control compound Ondasetron was used.

hERG binding studies were carried out at Bienta Enamine, Kiev, Ukraine. All experiments were performed using PredictorTM hERG Fluorescence Polarization Assay in accordance with the manufacturer’s protocol (Protocol PV5365) ([http://tools.invitrogen.com/content/sfs/manuals/Predictor_hERG_FP_Assay_man.pdf](http://tools.invitrogen.com/content/sfs/manuals/Predictor_hERG_FP_Assay_man.pdf)).

Fluorescence Polarization (FP) readout technology is based on the observation that when a small fluorescent molecule (the tracer) is excited by the polarized light, the emitted light is largely depolarized because of the rapid rotation of the molecule in the solution during its fluorescence lifetime. The hERG reaction is performed by incubating the tracer and membranes with hERG channel for 2-4 hours in the solution. The fluorescence polarization is maximal when nothing interferes with the reaction of the tracer and hERG membranes (minimal tracer rotation). But when a tested compound competes with the tracer for the hERG channel, the polarization of emitted light lowers due to the ability of free unbound tracer to rotate rapidly in the solution. The reference compound (E-4031, provided by the manufacturer) was used to validate assay performance. The calibration curve of the E-4031 was used to compare the IC<sub>50</sub> of E-4031 in the performed assay with the manufacturer’s provided data. “Sigmoidal dose-response (variable slope)” function of GraphPad Prism software was used for the calibration curve building and calculation of IC<sub>50</sub> for E-4031 assessment. IC<sub>50</sub> value for E-4031 was found to be approximately 70 nM in accordance with the published data. All test points for the compound were performed in quadruplicates. Three dilutions of the tested compound were assessed – 1 μM, 5 μM and 20 μM. The set of positive and negative controls (Assay blank – no tracer added, Assay Negative - 30 μM of E-4031 that represents 100 % tracer displacement and gives minimum assay polarization value) was performed with 4 repeats.

Plasma stability was determined at Bienta Enamine, Kiev, Ukraine. Incubations were carried out in 5 aliquots of 40 μL each (one for each time point), in duplicates. Test
compounds (1 μM, final DMSO concentration 1%) were incubated at 37°C with shaking at 100 rpm. Five time points over 120 minutes have been analyzed. The reactions were stopped by adding 200 μL of acetonitrile with subsequent plasma proteins sedimentation by centrifuging at 5500 rpm for 5 minutes. Supernatants were analyzed by the HPLC system coupled with tandem mass spectrometer. The percentage of the test compounds remaining after incubation in plasma and their half-lives (T1/2) were calculated.

Microsomal stability was determined at Bienta Enamine, Kiev, Ukraine. Mouse hepatic microsomes were isolated from pooled (50), perfused livers of BALB/c male mice according to the standard protocol (Hill, J.R. in Current Protocols in Pharmacology 7.8.1-7.8.11, Wiley Interscience, 2003). The batch of microsomes was tested for quality control using Imipramine, Propranolol and Verapamil as reference compounds. Microsomal incubations were carried out in 96-well plates in 5 aliquots of 40 μL each (one for each time point). Liver microsomal incubation medium contained PBS (100 mM, pH 7.4), MgCl₂ (3.3 mM), NADPH (3 mM), glucose-6-phosphate (5.3 mM), glucose-6-phosphate dehydrogenase (0.67 units/ml) with 0.42 mg of liver microsomal protein per ml. Control incubations were performed replacing the NADPH-cofactor system with PBS. Test compound (2 μM, final solvent concentration 1.6 %) was incubated with microsomes at 37°C, shaking at 100 rpm. Incubations were performed in duplicates. Five time points over 40 minutes had been analyzed. The reactions were stopped by adding 12 volumes of 90% acetonitrile-water to incubation aliquots, followed by protein sedimentation by centrifuging at 5500 rpm for 3 minutes. Supernatants were analyzed using the HPLC system coupled with tandem mass spectrometer.
Spectra

Methyl 2-[(4-[3-(benzyloxy)propoxy]phenyl)acetate (4a; ZHAWOC4496)

NMR
Methyl 2-\{4-\{3-(benzyloxy)propoxy\}phenyl\}acetate (4a; ZHAWOC4496)
Methyl 2-4-[3-(benzyloxy)propoxy]phenylacetate (4a; ZHAWOC4496)
Methyl 2-\{4-\{4-(benzyloxy)butoxy\}phenyl\}acetate (4b; ZHAWOC4534)
Methyl 2-{4-[4-(benzyloxy)butoxy]phenyl}acetate (4b; ZHAWOC4534)
Methyl 2-(4-(4-(benzyloxy)butoxy)phenoxy)acetate (4b; ZHAWOC4534)
Methyl 2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (4c; ZHAWOC5921)

NMR
Methyl 2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetate (4c; ZHAWOC5921)
Methyl 2-(4-[5-(benzyloxy)pentyl]oxy)phenyl)acetate (4c; ZHWOC5921)
Methyl 2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetate (4d; ZHAWOC5946)

NMR
Methyl 2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetate (4d; ZHAWOC5946)
Methyl 2-(4-(6-(benzyloxy)hexyl)oxy)phenyl)acetate (4d; ZHAWOC5946)
2-{4-[3-(benzyloxy)propoxy]phenyl}acetic acid (5a; ZHAWOC4497)
2-{4-[3-(benzyloxy)propoxy]phenyl}acetic acid (5a; ZHAWOC4497)
2-(4-(3-(benzyloxy)propoxy)phenyl)acetic acid (5a; 2HAWOC4497)
2-{4-[4-(benzyloxy)butoxy]phenyl}acetic acid (5b; ZHAWOC4535)

NMR
2-\{4-[4-(benzyloxy)butoxy]phenyl\}acetic acid (5b; ZHAWOC4535)
2-(4-(benzyloxy)butoxy)phenylacetic acid (5b, ZHAWOC4535)
2-((5-benzyloxy)pentyl)oxy)phenyl)acetic acid (5c; ZHAWOC5922)

NMR
2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetic acid (5c; ZHAWOC5922)
2-(4-(l-(benzyloxy)pentyl)oxy)phenyl)acetic acid (5c, ZHAWOC5922)
2-(4-{[6-(benzyloxy)hexyl]oxy}phenyl)acetic acid (5d; ZHAWOC5947)

NMR
2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetic acid (5d; ZHAWOC5947)
2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetic acid (5d; ZHAWOC5947)
5-amino-2-[(4-fluorophenyl)methyl]-2,3-dihydro-1H-isooindole-1,3-dione (7b; ZHAWOC3199)

NMR
5-amino-2-[(4-fluorophenyl)methyl]-2,3-dihydro-1H-isindole-1,3-dione (7b; ZHAWOC3199)
5-amino-2-[(4-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (7b); ZHAWOC3199
5-amino-2-[(3-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (7c; ZHAWOC6017)

NMR
5-amino-2-[(3-fluorophenyl)methyl]-2,3-dihydro-1H-isooindole-1,3-dione (7c; ZHAWOC6017)
5-amino-2-(3-fluorophenyl)methyl-2,3-dihydro-1H-isoindole-1,3-dione (7c)

HRMS
5-amino-2-[(2-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (7d; ZHAWOC1246)
5-amino-2-[(2-fluorophenyl)methyl]-2,3-dihydro-1H-isooindole-1,3-dione (7d; ZHAWOC1246)
5-amino-2-[(2-fluorophenyl)methyl]-2,3-dihydro-1H-isoindole-1,3-dione (7d)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-{4-[3-(benzyloxy)propoxy]phenyl}acetamide (8a; ZHAWOC4511)

NMR
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-[4-[3-(benzyloxy)propoxy]phenyl]acetamide (8a; ZHAWOC4511)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-(4-[3-((benzyloxy)propoxy)phenyl]acetamide (8a; ZHAWOC4511))
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoadol-5-yl)-2-[4-[4-(benzyloxy)butoxy]phenyl]acetamide (8b; ZHAWOC4752)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-[(benzyloxy)butoxy]phenyl]acetamide (8b; ZHAWOC4752)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindolin-5-yl)-2-(4-[4-(benzyloxy)butoxy]phenyl)acetamide (BB: ZHAWOC4752)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-(4-((5-(benzyloxy)pentyl)oxy)phenyl)acetamide (8c; ZHAWOC5979)

NMR
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)acetamide (8c; ZHAWOC5979)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-{[(benzyloxy)pentyl]oxy}phenyl)acetamide (8c: ZHAWOC5979)
2-((5-(benzyloxy)pentyloxy)phenyl)-N-(2-((4-fluorophenyl)methyl)-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)acetamide (8d; ZHAWOC5682)

NMR
2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)-N-[2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]acetamide (8d; ZHAWOC5682)
2-(4-(benzyloxy)pentyl)oxy)phenyl-N-[2-(4-fluorophenyl)methyl]-1,3-dihydro-1H-isoindol-5-ylacetamide (8d; ZHAWC5682)
2-(4-[[5-(benzyloxy)penty]oxy]phenyl)-N-[2-[(3-fluorphenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]acetamide (8e; ZHAWOC6018)

NMR
2-(4-((5-(benzyl)oxy)pentyl)oxy)phenyl)-N-[2-((3-fluorophenyl)methyl)-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]acetamide (8e; ZHAWOC6018)
2,4-(benzyloxy)pentyl[(phenyl)oxy]-N-[12-(3-fluorophenyl)methyl]-1,3-dihydro-1H-indol-5-ylacetamide (8e; ZHAWOC6018)

HRMS
2-(4-[[5-(benzyloxy)pentylox]oxy]phenyl)-N-[2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]acetamide (8f; ZHAWOC6019)

NMR
2-(4-[[5-(benzyloxy)pentyl]oxy]phenyl)-N-[2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H isoindol-5-yl]acetamide (8f; ZHAWOC6019)
2-(4-(benzyloxy)pentyl)oxy)phenyl-N-[2-(2-fluorophenyl)methyl]-1,3-dihydro-1H-isooindol-5-ylacetamide (8f; ZHAWOC6019)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetamide (8g; ZHAWOC5980)

NMR
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-(4-[[6-(benzyloxy)hexyl]oxy]phenyl)acetamide (8g; ZHAWOC5980)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-indol-5-yl)-2-(4-[(benzyloxy)hexyl]oxy)phenyl)acetamide (89; ZHAWOC5980)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-(3-hydroxypropoxy)phenyl]acetamide (9a; ZHAWOC4512)

NMR
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-(3-hydroxypropoxy)phenyl]acetamide (9a; ZHAWOC4512)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-indol-5-yl)-2-[4-(3-hydroxypropoxy)phenyl]acetamide (9a; ZHAWOC4512)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-(4-hydroxybutoxy)phenyl]acetamide (9b; ZHAWOC4753)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-[4-(4-hydroxybutoxy)phenyl]acetamide (9b; ZHAWOC4753)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-[4-(4-hydroxybutoxy)phenyl]acetamide (9b; ZHAWOC4753)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9c; ZHAWOC5130)

NMR
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)-2-[(5-hydroxypentyl)oxy]phenylacetamide (9c; ZHAWOC5130)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)-2,4-{5-[(5-hydroxypentyl)oxy]phenyl}acetamide (9c; ZHAWOC5130)
N-{2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9d; ZHAWOC5683)

NMR
N-2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9d; ZHAWOC5683)
N-[2-{4-(fluorophenyl)methyl}-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9d; Z-HAWOC5683)
N-[2-[(3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-2-[(5-hydroxypentyl)oxy]phenyl]acetamide (9e; ZHAWOC6021)

NMR
N-{2-[(3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl}-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9e; ZHAWOC6021)
N-[2-(3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-indol-5-yl]2-[4-(5-
hydroxyphenyl)oxy]phenyl]acetamide (9e; ZHAWOC6021)
N-(2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9f; ZHAWOC6022)
N-[2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]-2-{4-[(5-hydroxypentyl)oxy]phenyl}acetamide (9f; ZHAWOC6022)
N-[2-(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl] 2-(4-[5-
hydroxypentyl]oxy)phenyl)acetamide (9f; ZHAWOC602)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-\{(6-hydroxyhexyl)oxy\}phenylacetamide (9g; ZHAWOC5132)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-{4-[(6-hydroxyhexyl)oxy]phenyl}acetamide (9g; ZHAWOC5132)
N-(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)-2-(4-hydroxyhexyl)phenylacetamide (9g; ZHAWOC5132)
3-(4-[[2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl]methyl]phenoxyl)propanoic acid (2a; ZHAWOC4765)

NMR
3-(4-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)propanoic acid (2a; ZHAWOC4765)
3-((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)carbamoyl)methyl)phenoxy)propanoic acid (2a; ZHAWOC4765)

**HRMS**

| Retention | MS Source | Formula | Species | MZ | Score | DP (ppm) | Score (FDR) |
|-----------|-----------|---------|---------|----|-------|----------|-------------|
| 4.75      | RP-C18    | C29H42N2O6 | [M+H]+ | 459.3538 | 94.37 | 3.09 | 94.37 |

**IC<sub>50</sub>**

![Graph showing IC<sub>50</sub> for MMP13](image)
4-(4-[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)carbamoyl]methyl)phenoxy)butanoic acid (2b; ZHAWOC4766)

NMR
4-(4-[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-y1)carbamoyl]methyl)phenoxy)butanoic acid (2b; ZHAWOC4766)
4-(4-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl)carbamoyl)methyl)phenoxy)butanoic acid (2b; ZHAWOC4766)

**HRMS**

| Score | EIC Source | Formula | Species | n/z | Score | m/z (ppm) | Score (EIC) |
|-------|------------|---------|---------|-----|-------|-----------|------------|
|       |            |         |         |     |       |           |            |

**IC\textsubscript{50}**

![Graph showing compound IC\textsubscript{50} for MMP13](image)

| Compound | 4766 | 4766 | 4766 |
|----------|------|------|------|
| 4766     | -1.204 | -1.327 | -1.335 |
| 4766     | 5.095e-007 | 7.270e-007 | 4.312e-007 |

**HILLSLOPE**

| 4766 | 4766 | 4766 |
|------|------|------|
| 5.095e-007 | 7.270e-007 | 4.312e-007 |

**EC\textsubscript{50}**

| 4766 | 4766 | 4766 |
|------|------|------|
| 5.095e-007 | 7.270e-007 | 4.312e-007 |
5-(4-(((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)pentanoic acid (2c; ZHAWOC5131)

NMR
5-(4-((((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)methyl)phenoxy)pentanoic acid (2c; ZHAWOC5131)
5-[(4-[[{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)carbamoyl}methyl]phenoxy]pentanoic acid (2c; ZHAWOC5131)

HRMS

| S/N | Input (Mass) | Formula | species | m/z | score | dp (ppm) | score | dp (ppm) |
|-----|-------------|---------|---------|-----|-------|----------|-------|----------|
| 5531 | 407-1019    | C24H18N2O5 | 39+     | 407  | 1019  | 97.18    | 1.37  | 97.18    |

IC₅₀

**Compound IC₅₀ for MMP13**

| % Activity | Log [compound] (M) |
|------------|---------------------|
| 5131       | -1.151              |
| 5131       | -1.025              |
| 5131       | -1.151              |

HILLSLOPE: -1.151
EC₅₀: 3.613e-008, 3.475e-008, 3.492e-008
5-{4-[(2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl)methyl]phenoxy}pentanoic acid (2d; ZHAWOC5684)

NMR
5-[(2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl)methyl]phenoxy]pentanoic acid (2d; ZHAWOC5684)
5-{4-[(2-[(4-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl)methyl]phenoxy}pentanoic acid (2d; ZHAWOC5684)

HRMS

IC\textsubscript{50}

Compound IC\textsubscript{50} for MMP 13

| % Activity | Log [compound] (M) |
|------------|-------------------|
| 120        | -9                |
| 100        | -8                |
| 80         | -7                |
| 60         | -6                |
| 40         | -5                |
| 20         | -4                |

HILLSLOPE
EC\textsubscript{50}

|            | 5684         | 5684         | 5684         |
|------------|--------------|--------------|--------------|
| HILLSLOPE  | -0.4789      | -0.5361      | -0.4540      |
| EC\textsubscript{50} | 3.835e-009 | 9.790e-009 | 5.316e-009 |
5-[(2-[[3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl)methyl]phenoxy]pentanoic acid (2e; ZHAWOC6023)

NMR
5-{4-[[2-[(3-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl]carbamoyl]methyl]phenoxy}pentanoic acid (2e; ZHAWOC6023)
5-[(2-[[3-fluorophenyl]methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl)methyl]phenoxy]pentanoic acid (2e; ZHAWOC6023)

HRMS

IC₅₀

Compound IC₅₀ for MMP13

| Compound | IC₅₀ (M) |
|----------|---------|
| 6023     | 8.966e-009 |
| 6023     | 1.261e-008 |
| 6023     | 9.848e-009 |
5-{4-[[2-[[2-fluorophenyl]methyl]-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl]carbamoil]methyl]phenoxy}pentanoic acid (2f; ZHAWOC6024)

NMR
5-{4-[(2-[2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl)methyl]phenoxy}pentanoic acid (2f; ZHAWOC6024)
5-\{4-[[2-[(2-fluorophenyl)methyl]-1,3-dioxo-2,3-dihydro-1H-isooindol-5-yl]carbamoyl[methyl]phenoxy]pentanoic acid (2f; ZHAWOC6024)

**HRMS**

| MZ | Formula | Charge | Purity |
|----|---------|--------|--------|
| 365.1533 | C23H19N3O7S | 1+ | 97.14 |

**IC\textsubscript{50}**

![Graph of Compound IC\textsubscript{50} for MMP13](image)

| Compound | 6024 | 6024 | 6024 |
|----------|------|------|------|
| EC\textsubscript{50} | 1.886e-007 | 1.132e-007 | 1.015e-007 |
| HILLSLOPE | -0.7726 | -0.6255 | -0.7095 |
6-[(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isouindol-5-yl)carbamoyl]methyl|phenoxo)hexanoic acid (2g; ZHAWOC5133)

NMR
6-(4-((((2-benzyl-1,3-dioxo-2,3-dihydro-1H-isoindol-5-yl)carbamoyl)ethyl)phenoxy)hexanoic acid (2g; ZHAWOC5133)
6-(4-{{(2-benzyl-1,3-dioxo-2,3-dihydro-1H-isindol-5-yl)carbamoyl}methyl}phenoxy)hexanoic acid (2g; ZHAWOC5133)

HRMS

| Scan | m/z | Intensity | Q1 | Q2 | Q3 | Charge | Mass Accuracy (ppm) | Score |
|------|-----|-----------|----|----|----|--------|---------------------|-------|
| 200  | 301 | 10000     | 100| 100| 0  | 1+     | 301.2077            | 38.80 |

IC_{50}

**Compound IC50 for MMP13**

- **HILLSLOPE**
  - 5133: -1.047
  - 5133: -0.8992
  - 5133: -1.271

- **EC50**
  - 5133: 1.478e-007
  - 5133: 1.136e-007
  - 5133: 1.901e-007