Electronic Supplementary Information

Topological effects in ultrafast photoinduced processes between flurbiprofen and tryptophan in linked dyads and within human serum albumin

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**Fig. S17** Geometry optimized (HyperChem Release 8.0.3 for Windows Molecular Model System, PM3) structures for (S,S)-2 (A) and (R,S)-2 (B).
**Fig. S18** A) LFP spectra for (S)-FBP (black), (S,S)-2 (dark red) and (R,S)-2 (dark blue) 0.2 µs after the laser pulse. B) Decay traces at 370 nm. All measurements were performed in deaerated acetonitrile at $\lambda_{\text{exc}} = 266$ nm.

**Fig. S19** Femtosecond transient absorption spectra from 1 ps (black) to 2 ns (green) for FBP (A) and HSA (B) after excitation at 250 nm in aqueous PBS.

**Fig. S20** Normalized absorption and emission spectra for HSA (gray) and FBP (black), respectively, in aqueous PBS. The fluorescence spectrum was measured at $\lambda_{\text{exc}} = 266$ nm.
EXPERIMENTAL SECTION

Chemicals and reagents. (S)- and (R)-flurbiprofen, (S)-tryptophan methyl ester, (1S,3R)-3-aminocyclopentanecarboxylic acid, 8-aminooctanoic acid, 1-hydroxybenzotriazole (BtOH), N,N'-dicyclohexylcarbodiimide (DCC), N-hydroxysuccinimide (NHS), 1-(3-dimethylaminopropyl)-N-ethylcarbodiimide hydrochloride (EDC), sodium hydrogen carbonate (NaHCO₃) and human serum albumin were purchased from Sigma-Aldrich. Tetrahydrofuran (THF), pyridine, methylene chloride, ethyl acetate and acetonitrile (HPLC quality) were from Scharlab. PBS buffer was prepared by dissolving phosphate-buffered saline tablets (Sigma) using ultrapure water from a Millipore (Milli-Q Synthesis) system.

A semipreparative JASCO HPLC system (PU-2080 Plus pump, DG-2080-54-line degasser and LG-2080-04 gradient unit) connected to a JASCO (UV-1575) detector was used to further purify the different products, using an isocratic flux (2 mL/min) of the appropriate organic solvent as an eluent, and a SEA18 Teknokroma column or a Tecknokroma TR-016178 NF-33978 Tracer Excel 120 31 column, 5 μm (25 × 1 cm²).

Spectroscopic Techniques. The ¹H- and ¹³C-NMR spectra were recorded at 400 and 100 MHz, respectively, using a Bruker AVANCE III instrument; chemical shifts are reported in ppm.

High-resolution mass spectrometry (HRMS) was performed in an Ultra Performance Liquid Chromatography (UPLC) ACQUITY system (Waters Corp.) with a conditioned autosampler at 4 °C. The separation was accomplished on an ACQUITY UPLC BEH C18 column (50 mm × 2.1 mm i.d., 1.7 μm), which was maintained at 40 °C. The analysis was performed using acetonitrile and water (60:40 v/v containing 0.01% formic acid) as the mobile phase with a flow rate of 0.5 mL/min, and injection volume was 5 μL. The Waters
ACQUITY™ XevoQToF Spectrometer (Waters Corp.) was connected to the UPLC system via an electrospray ionization (ESI) interface. This source was operated in positive ionization mode with the capillary voltage at 1.5 kV at 100 °C and the temperature of the desolvation was 300 °C. The cone and desolvation gas flows were 40 L h\(^{-1}\) and 800 L h\(^{-1}\), respectively. The collision gas flow and collision energy applied were 0.2 mL/min and 12 V, respectively. All data collected in Centroid mode were acquired using Masslynx™ software (Waters Corp.). Leucine- enkephalin was used at a concentration of 500 pg/μL as the lock mass generating an [M + H]\(^+\) ion (m/z 556.2771) and fragment at m/z 120.0813 and flow rate of 50 μL/min to ensure accuracy during the MS analysis.

Steady-state absorption spectra were recorded in a JASCO V-760 spectrophotometer. Steady-state fluorescence measurements (\(\lambda_{\text{exc}} = 266\) nm) were performed on an Edinburgh FS5 spectrofluorometer, provided with a monochromator in the wavelength range of 200-900 nm. Time-resolved fluorescence measurements were done using an EasyLife X system containing a sample compartment composed of an automated Peltier cuvette holder to control the temperature at 24 °C, a pulsed LED excitation source and a lifetime detector. The employed LED excitation source was 265 nm, with emission filter of WG305 and/or WG420. The absorbance of the samples was identical (ca. 0.1) at the excitation wavelength.

Laser Flash Photolysis (LFP) measurements were performed using a pulsed Nd:YAG L52137 V LOTIS TII at \(\lambda_{\text{exc}} = 266\) nm. The single pulses were ca. 10 ns duration, and the energy was ~12 mJ/pulse. The laser flash photolysis system consisted of the pulsed laser, a 77250 Oriel monochromator and an oscilloscope DP04054 Tektronix. The output signal from the oscilloscope was transferred to a personal computer. Absorbances of all solutions were adjusted at ~0.20 at 266 nm in acetonitrile (HPLC grade). All UV,
fluorescence and LFP measurements were done using 10 × 10 mm² quartz cuvettes at room temperature in deaerated acetonitrile (25 min N₂ bubbling). Control experiments indicated that the degree of decomposition of the samples after photolysis was lower than 5%.

Femtosecond transient absorption experiments were performed using a pump-probe system. The femtosecond pulses were generated with a mode-locked Ti-Sapphire laser of a compact Libra HE (4 W power at 4 kHz) regenerative amplifier delivering 100 fs pulses at 800 nm (1 mJ/pulse). The output of the laser was split into two parts to generate the pump and the probe beams. Thus, tunable femtosecond pump pulses were obtained by directing the 800 nm light into an optical parametric amplifier (OPA). In the present case, the 800 nm beam was transformed into the 250 nm exciting beam after performing proper alignment of the BBO crystals, optimizing the values of the two delay lines and using the appropriate mixers within the OPA. The 250 nm pump beam passed through a chopper prior to focus onto a rotating cell (1 mm optical path) containing the sample. The white light used as probe was produced after part of the 800 nm light from the amplifier travelled through a computer controlled 8 ns variable optical delay line and impinge on a CaF₂ rotating crystal. This white light was in turn split in two identical portions to generate reference and probe beams that then were focused on the rotating cell containing the sample. The pump and the probe beams were made to coincide to interrogate the sample. The power of the pump beam was set to 180 µW. Under these conditions, the degree of photodegradation of the samples was lower than 5%. A computer-controlled imaging spectrometer was placed after this path to measure the probe and the reference pulses to obtain the transient absorption decays/spectra. The experimental data were treated and compensated by the chirp using the ExciPro program. The data files were exported as matrix format from ExciPro to be treated with OriginLab program to get the time-resolved
spectra and the ultrafast decay traces, which were fitted using a multi-exponential function following the Levenberg-Marquardt iteration algorithm:

$$ F(t, \lambda) = \sum_{i=1}^{n} a_i(\lambda)e^{(-t/\tau_i)} + y_0 $$

with n = 2 or 3.

**Synthesis of dyads (S,S)-1 and (R,S)-1.** To a solution of (S)- or (R)-FBP-CSp (0.47 mmol) in methylene chloride (20 mL), 0.6 mmol of EDC and 0.6 mmol of BtOH were added. The mixture was maintained under stirring at room temperature, and then 0.6 mmol of (S)-TrpMe in 2 mL of methylene chloride were added dropwise. After 3 h, the crude was washed consecutively with diluted NaHCO₃, 1 M HCl, and brine, and then dried over MgSO₄. Final purification was performed by preparative layer chromatography (methylene chloride/ethyl acetate, 90/10, v/v), followed by recrystallization.

**N-[(1S,3R)-3-(2-(S)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)cyclopentane-1-carbonyl]-(S)-tryptophan methyl ester, (S,S)-1.** ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 7.52 – 7.48 (m, 3H), 7.42 – 7.31 (m, 6H), 7.21 – 7.16 (m, 3H), 7.11 – 7.07 (m, 1H), 6.89 (s, 1H), 6.11 (d, 1H, J = 8.0 Hz), 4.93 (m, 1H), 4.34 (m, 1H), 3.71 (s, 3H), 3.55 (q, 1H, J = 7.2 Hz), 3.34 – 3.24 (m, 2H), 2.60 (m, 1H), 1.94 – 1.73 (m, 4H), 1.67 – 1.56 (m, 2H), 1.52 (d, 3H, J = 7.2 Hz). ¹³C NMR (100 MHz, CDCl₃) δ 177.4, 172.8, 172.4, 161.1, 158.6, 143.6, 136.2, 135.8, 130.8, 129.1, 128.5 (x2), 127.8, 127.7, 127.5, 123.7, 122.8, 122.4, 119.8, 118.6, 115.4, 111.5, 109.9, 53.2, 52.6, 51.3, 46.8, 43.6, 35.9, 34.1, 29.0, 27.6, 18.4. Yield: 38%. HRMS (ESI): m/z calcd. for C₃₅H₃₅FN₃O₄ [M + H]⁺: 556.2653, found: 556.2658.
**N-[(1S,3R)-3-(2-(R)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)cyclopentane-1-carbonyl]-(S)-tryptophan methyl ester, (R,S)-1.**

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.29 (s, 1H), 7.54 – 7.51 (m, 3H), 7.43 – 7.34 (m, 6H), 7.21 – 7.10 (m, 4H), 6.93 (s, 1H), 6.09 (d, 1H, $J = 8.0$ Hz), 4.91 (m, 1H), 4.32 (m, 1H), 3.69 (s, 3H), 3.54 (q, 1H, $J = 7.2$ Hz), 3.36 – 3.25 (m, 2H), 2.60 (m, 1H), 1.93 – 1.84 (m, 2H), 1.78 – 1.66 (m, 4H), 1.54 (d, 3H, $J = 7.2$ Hz).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 177.4, 172.9, 172.4, 161.1, 158.6, 143.3, 136.3, 135.8, 130.8, 129.1, 128.5 ($\times 2$), 127.8, 127.6, 127.5, 123.7, 122.9, 122.5, 119.8, 118.7, 115.2, 111.5, 110.0, 53.2, 52.6, 51.3, 47.0, 43.7, 36.1, 34.2, 29.0, 27.8, 18.5. Yield: 42%.

HRMS (ESI): m/z calcd. for C$_{33}$H$_{35}$FN$_3$O$_4$ [M + H]$^+$: 556.2653, found: 556.2648.

**Synthesis of the intermediate (S)- and (R)-FBP-LSp.** To a solution of (S)- or (R)-FBP (1.23 mmol) in THF at 0 ºC, a solution of DCC (1.5 mmol) in THF was added dropwise; the mixture was kept under stirring for 20 min. NHS (1.5 mmol) in THF was added and the reaction mixture was kept 24h at room temperature. The resulting crude was added dropwise to a solution of 8-aminooctanoic acid (1.5 mmol) in aqueous NaHCO$_3$ (3 mmol) and kept stirring at room temperature for 2 hours. The solution was filtered and THF was evaporated under reduced pressure. The pH of the resulting aqueous layer was set at 5 by addition of HCl. Several consecutive extractions with ethyl acetate ($\times 3$) were performed, and the combined organic layers were washed with brine and then dried over anhydrous MgSO$_4$. Final purification was performed by silica gel column chromatography (ethyl acetate/methylene chloride 40/60) followed by an additional purification with semipreparative HPLC using an isocratic flux (2 mL/min) of MeCN as an eluent, and a SEA18 Teknokroma column, 5 μm (25 × 1 cm$^2$).

8-(2-(S)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)octanoic acid, (S)-FBP-LSp. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 – 7.53 (m, 2H), 7.46 – 7.35 (m, 4H), 7.16 – 7.10 (m, 2H), 5.40 (m, 1H), 3.58 (q, 1H, $J = 7.2$ Hz), 3.22 (q, 2H, $J = 7.2$ Hz), 2.32 (t, 2H, $J = 7.2$ Hz),
1.64 – 1.56 (m, 2H), 1.54 (d, 3H, J = 7.2 Hz), 1.48 – 1.41 (m, 2H), 1.33 – 1.22 (m, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 177.5, 173.5, 160.1, 158.6, 142.9, 135.4, 131.1, 128.9, 128.5 (×2), 127.4, 123.6, 115.4, 115.2, 46.8, 39.7, 33.6, 29.4, 28.9, 28.6, 26.5, 24.6, 18.6.

Yield: 55%. HRMS (ESI): m/z calcd. for C$_{23}$H$_{29}$FNO$_3$ [M + H]$^+$: 386.2138, found: 386.2135.

8-(2-(R)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)octanoic acid, (R)-FBP-LSp.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.55 – 7.52 (m, 2H), 7.46 – 7.35 (m, 4H), 7.16 – 7.10 (m, 2H), 5.44 (m, 1H), 3.56 (q, 1H, J = 7.2 Hz), 3.21 (q, 2H, J = 7.2 Hz), 2.31 (t, 2H, J = 7.2 Hz), 1.63 – 1.58 (m, 2H), 1.54 (d, 3H, J = 7.2 Hz), 1.48 – 1.41 (m, 2H), 1.29 – 1.22 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 178.3, 173.5, 160.0, 158.6, 142.8, 135.4, 131.0, 128.9, 128.5 (×2), 127.7, 123.6, 115.4, 115.2, 46.7, 39.7, 33.8, 29.4, 28.8, 28.7, 26.5, 24.5, 18.5. Yield: 60%. HRMS (ESI): m/z calcd. for C$_{23}$H$_{29}$FNO$_3$ [M + H]$^+$: 386.2138, found: 386.2131.

**Synthesis of dyads (S,S)-2 and (R,S)-2.** To a solution of (S)- or (R)-FBP-LSp (0.4 mmol) in pyridine (20 mL), 0.6 mmol of EDC and 0.6 mmol of BtOH were added. The mixture was maintained under stirring at room temperature, and then 0.6 mmol of (S)-TrpMe in 2 mL of pyridine were added dropwise. The mixture was kept under stirring overnight. The organic solvent was evaporated under reduced pressure, and the crude was dissolved in methylene chloride. Then, it was washed consecutively with diluted NaHCO$_3$, 1 M HCl, and brine, and then dried over MgSO$_4$. Final purification was performed by preparative layer chromatography (methylene chloride/ethyl acetate, 60/40, v/v), followed by an additional purification with semipreparative HPLC using an isocratic flux (2 mL/min) of methylene chloride/ethyl acetate (60/40, v/v) as an eluent, and a Tecknokroma TR-016178 NF-33978 Tracer Excel 120 31 column, 5 μm (25 × 1 cm$^2$).
N-[8-(2-(S)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)octanoyl]-(S)-tryptophan methyl ester, (S,S)-2. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.62 (s, 1H), 7.54 – 7.50 (m, 3H), 7.46 – 7.34 (m, 5H), 7.20 – 7.08 (m, 4H), 6.98 (m, 1H), 5.95 (d, 1H, $J = 7.6$ Hz), 5.51 (m, 1H), 4.96 – 4.91 (m, 1H), 3.70 (s, 3H), 3.57 (q, 1H, $J = 7.2$ Hz), 3.36 – 3.26 (m, 2H), 3.24 – 3.18 (m, 2H), 2.17 – 2.05 (m, 2H), 1.79 – 1.59 (m, 2H), 1.56 (d, 3H, $J = 7.2$ Hz), 1.55 – 1.40 (m, 2H), 1.33 – 1.18 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.6, 172.7, 172.5, 161.0, 158.6, 142.8, 136.2, 135.3, 131.1, 128.9, 128.5 (x2), 127.7, 127.6, 123.6, 122.8, 122.1, 119.5, 118.5, 115.4, 115.2, 111.4, 109.8, 52.7, 52.3, 46.7, 39.8, 36.3, 29.7, 29.4, 28.6, 27.6, 26.4, 25.2, 18.5. Yield: 32%. HRMS (ESI): m/z calcd. for C$_{35}$H$_{41}$FN$_3$O$_4$ [M + H]$^+$: 586.3086, found: 586.3084.

N-[8-(2-(R)-(2-fluoro-[1,1'-biphenyl]-4-yl)propanamido)octanoyl]-(S)-tryptophan methyl ester, (R,S)-2. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.64 (s, 1H), 7.54 – 7.51 (m, 3H), 7.46 – 7.34 (m, 5H), 7.20 – 7.08 (m, 4H), 6.97 (m, 1H), 5.94 (d, 1H, $J = 8.0$ Hz), 5.52 (m, 1H), 4.96 – 4.91 (m, 1H), 3.70 (s, 3H), 3.57 (q, 1H, $J = 7.2$ Hz), 3.37 – 3.27 (m, 2H), 3.21 (q, 2H, $J = 6.8$ Hz), 2.14 – 2.06 (m, 2H), 1.56 (d, 3H, $J = 7.2$ Hz), 1.53 – 1.48 (m, 2H), 1.45 – 1.37 (m, 2H), 1.26 – 1.20 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.6, 172.7, 172.5, 161.0, 158.5, 142.8, 136.2, 135.3, 131.0, 128.9, 128.5 (x2), 127.7, 127.6, 123.6, 122.8, 122.1, 119.5, 118.4, 115.4, 115.1, 111.4, 109.8, 52.7, 52.3, 46.7, 39.7, 36.3, 29.7, 29.4, 28.6, 27.6, 26.4, 25.2, 18.6. Yield: 30%. HRMS (ESI): m/z calcd. for C$_{35}$H$_{41}$FN$_3$O$_4$ [M + H]$^+$: 586.3086, found: 586.3082.
Fig. S1 $^1$H- and $^{13}$C-NMR for (S,S)-1 in CDCl$_3$. 
Fig. S2 $^1$H- and $^{13}$C-NMR for (R,S)-1 in CDCl$_3$. 
Fig. S3 $^1$H- and $^{13}$C-NMR for (S)-FBP-LSp in CDCl$_3$. 
Fig. S4 $^1$H- and $^{13}$C-NMR for (R)-FBP-LSp in CDCl$_3$. 
Fig. S5 $^1$H- and $^{13}$C-NMR for (S,S)-2 in CDCl$_3$. 
Fig. S6 $^1$H- and $^{13}$C-NMR for (R,S)-2 in CDCl$_3$. 
**Fig. S7** A) Normalized absorption spectra for FBP (black), Trp (gray), (S,S)-1 (red) and (R,S)-1 (blue). B) Normalized excitation spectra for FBP at $\lambda_{em} = 305$ nm (black), Trp at $\lambda_{em} = 345$ nm (gray) and (S,S)-1 (red) and (R,S)-1 at $\lambda_{em} = 400$ nm (blue). C) Normalized excitation spectra for (S,S)-1 (red) and (R,S)-1 at $\lambda_{em} = 450$ nm (blue). All measurements were performed in acetonitrile.
**Fig. S8** Fluorescence spectra for (S)-FBP (black), (S)-TrpMe (gray), (S,S)-1 (red) and (R,S)-1 (blue) after excitation at 250 nm in acetonitrile. The simulated spectrum that is obtained considering the percentage of photons absorbed by isolated FBP (90%) and TrpMe (10%) at 250 nm and assuming no interactions between them in their excited states is shown in violet.
**Fig. S9** A) Femtosecond transient absorption spectra for (S)-FBP from 1 ps (black) to 2 ns (green) after excitation at 250 nm in acetonitrile. B) Decay trace at 425 nm.
**Fig. S10** Femtosecond transient absorption spectra for (S)-TrpMe from 1 to 500 ps after excitation at 250 nm in acetonitrile.
Fig. S11 Femtosecond transient absorption spectra for (R,S)-1 from 1 ps (black) to 0.5 ns (green) after excitation at 250 nm in acetonitrile.
Table S1. Kinetic parameters ($\lambda_{exc} = 250$ nm) derived from the fits of the ultrafast transient absorption decay traces at 425 nm; $p_i$ represents the weight of each time constant $\tau_i$ in ps ($p_i = a_i \tau_i / \Sigma a_i \tau_i$).

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$^a$ This component, decaying in the ns time scale, was determined with higher uncertainty than the other two.
**Fig. S12** Geometry optimized (HyperChem Release 8.0.3 for Windows Molecular Model System, PM3) structures for \((S,S)-1\) (A) and \((R,S)-1\) (B).
Fig. S13 A) LFP spectra for (S)-FBP (black), (S,S)-1 (red) and (R,S)-1 (blue) 0.2 μs after the laser pulse. B) Decay traces at 370 nm. All measurements were performed in deaerated acetonitrile at λ_{exc} = 266 nm.
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Fig. S19 Femtosecond transient absorption spectra from 1 ps (black) to 2 ns (green) for FBP (A) and HSA (B) after excitation at 250 nm in aqueous PBS.
**Fig. S20** Normalized absorption and emission spectra for HSA (gray) and FBP (black), respectively, in aqueous PBS. The fluorescence spectrum was measured at $\lambda_{exc} = 266$ nm.