Supplementary Information

A controlled release system for long-acting intravitreal delivery of small molecules

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I. Chemical Syntheses

\((1R,3S,5R)-\text{N}^2-5\text{-}(2\text{-aminoethoxy})-1\text{-carbamoyl-indol-3-yl}]-\text{N}^2-\text{(3-chloro-2-fluorophenyl)methyl}-2\text{-azabicyclo[3.1.0]hexane-2,3-dicarboxamide}\) (4): A solution of \((1R,3S,5R)-\text{N}^2-5\text{-carbamoyl-5-}(\text{cyanomethoxy})\text{indol-3-yl}]-\text{N}^2-\text{(3-chloro-2-fluorophenyl)methyl}-2\text{-azabicyclo[3.1.0]hexane-2,3-dicarboxamide}\) (WO2012093101, e.g. 373; 0.016 g, 0.030 mmol), HCl (0.030 mL) and \(\text{EtOH}\) (0.30 mL) was stirred at rt under \(\text{H}_2\) atmosphere (balloon pressure). After being stirred for 30 h at rt, the reaction mixture was filtered with a celite pad using a mixture of \(\text{EtOH}\) and \(\text{EtOAc}\). The filtrate was diluted with saturated aqueous \(\text{NaHCO}_3\), and extracted with \(\text{EtOAc}\). The extracts were washed with \(\text{HCl}\) (0.030 mL) and \(\text{H}_2\text{O}\). After being dried over \(\text{Na}_2\text{SO}_4\) and concentrated. The residue was purified by column chromatography on aminated silica gel (EtOAc/MEOH) to afford 4 (0.0035 g, 0.0066 mmol, 22%) as a colorless solid. \(^1\text{H}\) NMR (500 MHz, \(\text{CD}_3\text{OD}, \text{TMS} = 0.00\)) \(\delta 0.65-0.70\) (m, 1H), 1.00–1.07 (m, 1H), 1.83–1.91 (m, 1H), 2.26–2.34 (m, 1H), 2.41–2.48 (m, 1H), 3.02 (t, \(J = 5.4\) Hz, 2H), 3.63–3.68 (m, 1H), 3.99–4.09 (m, 2H), 4.33 (dd, \(J = 5.9, 9.3\) Hz, 1H), 4.45 (d, \(J = 15.6\) Hz, 1H), 4.52 (d, \(J = 3.0\) Hz, 1H, 6.96 (dd, \(J = 2.4, 9.3\) Hz, 1H), 7.04–7.09 (m, 1H), 7.19 (d, \(J = 2.4\) Hz, 1H), 7.31–7.37 (m, 2H), 7.73 (s, 1H), 8.14 (d, \(J = 8.8\) Hz, 1H)

MS (ESI) \(m/z\): 529 [M+H]^+.

\(\text{tert-Butyl 4-pentenoate}\) (5). Concentrated \(\text{H}_2\text{SO}_4\) (6.0 mL, 110 mmol) was added dropwise to a stirred suspension of anhydrous \(\text{MgSO}_4\) (35.0 g) in \(200\) mL of \(\text{CH}_2\text{Cl}_2\). After stirring for 15 min, 4-pentenoic acid (10.2 mL, 100 mmol) was added, followed by tert-butanol (48.0 mL, 500 mmol). The flask was sealed and stirred for 48 hr at ambient temperature. The suspension was filtered through Celite, and the filtrate was washed with 1 M \(\text{Na}_2\text{CO}_3\), water, and brine. After drying over \(\text{MgSO}_4\), the crude product was filtered through a pad of \(\text{SiO}_2\), and concentrated to provide the title compound (13.5 g, 86 mmol, 86% yield) as a yellow oil. \(\text{bp}^{20\text{mm}} 58-60\) °C.

\((\text{S)}\)-\(\text{tert-Butyl 4,5-epoxypentanoate}\) (6). Solid 75% mCPBA (28.0 g, 122 mmol) was added to a stirred solution of tert-butyl 4-pentenoate (7) (15.6 g, 100 mmol) in 200 mL of \(\text{CH}_2\text{Cl}_2\). After 16 hr at ambient temperature, the suspension was diluted with 200 mL of hexane and filtered. The filtrate was washed 2x sat. \(\text{NaHCO}_3\), water, and brine, then dried over \(\text{MgSO}_4\), filtered and concentrated. The resulting oil was taken up in hexane, filtered, and applied to a \(\text{SiO}_2\) column. Elution with 5% \(\text{EtOAc/hexane}\) provided \(\text{tert-butyl 4,5-epoxypentanoate}\) (12.4 g, 72 mmol, 72% yield) as a colorless oil.

A mixture of \((\text{R,R})\)-\text{N,N'}-bis(3,5-di-\text{butylsalicylidene})-1,2-cyclohexanediaminecobalt(II) (100 mg, 0.166 mmol, 0.005 Eq) and acetic acid (0.040 mL, 0.68 mmol, 0.021 Eq) in THF (5 mL) was stirred for 30 min under air exposure. Racemic tert-butyl 4,5-epoxypentanoate (5.56 g, 32.3 mmol, 1 Eq) was added, the mix was cooled on ice, and water (0.32 mL, 17.8 mmol, 0.55 Eq) was added. The mixture was allowed to warm slowly to ambient temperature and stirred 24 hr,
then diluted with hexane, filtered through a pad of SiO$_2$ (20% EtOAc/hexane) and concentrated. The crude product was purified by chromatography on SiO$_2$ with a gradient of 0 – 20% EtOAc/hexane to provide 2.52 g (100% of expected) of a pale yellow oil. Analysis of chiral purity was performed after conversion to linker-HSC 8A (below). The configuration is assumed to be (S) based on the reported catalyst selectivity.

(R)-tert-Butyl 4-hydroxy-5-(methylsulfonyl)pentanoate (7A). Sodium methanesulfonate (1.20 g, 12 mmol) was dissolved in 1.2 mL of water. Ethanol (10 mL) and acetic acid (0.35 mL) were added, followed by (S)-tert-butyl 4,5-epoxypentanoate 6 (1.00 g, 5.8 mmol). The reaction was kept at a gentle reflux for 4 h. After cooling ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with sat. NaHCO$_3$, water, and brine. After drying over MgSO$_4$, the organic phase was filtered and concentrated to an oil, which crystallized upon standing. Recrystallization from 30% EtOAc/hexanes provided the title compound (0.78 g, 3.1 mmol, 53% yield) as a crystalline solid.

(R)-tert-Butyl 4-hydroxy-5-cyanopentanoate (7B). Sodium cyanide (1.00 g, 20 mmol) and ammonium chloride (1.0 g, 18 mmol) were dissolved in 3.4 mL of water and 6.6 mL of ethanol (6.6 mL). (S)-tert-butyl 4,5-epoxypentanoate 6 (2.90 g, 16.9 mmol) was added, and the mixture was stirred 16 h at ambient temperature. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with 5% KHSO$_4$, water, and brine. After drying over MgSO$_4$, the organic phase was filtered and concentrated to an oil, which was chromatographed on SiO$_2$ (0-50% EtOAc/hexane) to provide a colorless oil that crystallized upon standing (2.16 g, 10.8 mmol, 64% yield).

(R)-O-[tert-Butyl 5-(methylsulfonyl)pentanoate-4-y]-O'-succinimidyl carbonate (8A). Pyridine (0.16 mL, 2.0 mmol) was added dropwise to a solution of (R)-tert-butyl 4-hydroxy-5-(methylsulfonyl)pentanoate 7A (252 mg, 1.0 mmol) and triphosgene (500 mg, 1.7 mmol) in 15 mL of THF. After stirring for 10 min, the mixture was filtered and concentrated. The residue was taken up in 15 mL of THF, and N-hydroxysuccinimide (230 mg, 2.0 mmol) and pyridine (0.25 mL, 3.1 mmol) were added. After 10 min, the mixture was diluted with EtOAc, washed with water, 5% KHSO$_4$, and brine, then dried over MgSO$_4$, filtered, and evaporated. The residue was crystallized from 1:1 EtOAc/hexane to provide the title compound (280 mg, 0.71 mmol, 71% yield). Optical purity was assessed by reaction with octreotide, which provides diastereomeric products that are resolved by HPLC.

(R)-O-[tert-Butyl 5-cyanopentanoate-4-y]-O'-succinimidyl carbonate (8B). Pyridine (0.40 mL, 5.0 mmol) was added dropwise to a solution of (R)-tert-butyl 4-hydroxy-5-cyanopentanoate 7B (500 mg, 2.5 mmol) and triphosgene (1.25 g, 4.2 mmol) in 25 mL of THF. After stirring for 10 min, the mixture was filtered and concentrated. The residue was taken up in 25 mL of THF, and N-hydroxysuccinimide (625 mg, 5.4 mmol) and pyridine (0.625 mL, 7.8 mmol) were added. After 10 min, the mixture was diluted with EtOAc, washed with water, 5% KHSO$_4$, and brine, then dried over MgSO$_4$, filtered, and evaporated. The residue was crystallized from 1:1 EtOAc/hexane to provide the title compound (612 mg, 1.8 mmol, 72% yield).

Linker-Drug ester 9A: A solution of 8A (17.8 mg, 45 umol, 1.1 Eq) in 100 μL of DMF was added to a solution of 4 (21 mg, 40 umol, 1 Eq) in 1 mL of DMF, followed by N,N-diisopropylethylamine (7 μL, 40 umol, 1 Eq). After 1 h at ambient temperature, the reaction was complete as determined by HPLC analysis, and the mixture was concentrated to dryness under vacuum. The residue was chromatographed on SiO$_2$ using a step gradient of hexane, 1:2, 1:1, and 2:1 acetone/hexane, and acetone to provide the product (30.8 mg, 38 umol, 96%) as a colorless glass. LC/MS shows single peak having [M+H]$^+$ = 807.32, calc. for C$_{36}$H$_{45}$ClF$_{6}$N$_{6}$O$_{10}$S$^+$ = 807.25.
**Linker-Drug ester 9B:** N,N-diisopropylethylamine (64 μL of 100 mM in MeCN, 6.4 umol, 1 Eq) was added to a mixture of 8B (2 mg, 10 umol, 1.6 Eq) and 4 (3.4 mg, 6.4 umol, 1 Eq) in 1 mL of MeCN. After 1 hr at ambient temperature, the reaction was complete as determined by HPLC analysis, and the mixture was concentrated to dryness under vacuum. LC/MS shows single peak having [M+H]⁺ = 754.3, calc. for C₃₆H₄₂ClFN₇O₈⁺ = 754.2. UV analysis indicated 6.4 umol of product (100%). This material was used without further purification.

**Linker-Drug 10A:** The ester 9A (30.8 mg, 38 umol) was dissolved in 1 mL of 90:10 CF₃CO₂H/H₂O cooled on ice. After 30 min, the mixture was warmed to ambient temperature and concentrated to dryness under vacuum. The residue was washed 2x with MTBE, then dried overnight over KOH pellets under high vacuum to provide the product (24.8 mg, 33 umol, 87%). LC/MS shows single peak having [M-H]⁻ = 749.5, calc. for C₃₂H₃₅ClFN₆O₁₀S⁻ = 749.18.

**Linker-Drug 10B:** The crude ester 9B (6.4 umol by UV) was dissolved in 1 mL of 90:10 CF₃CO₂H/H₂O cooled on ice. After 30 min, the mixture was warmed to ambient temperature and concentrated to dryness under vacuum. The residue was washed 2x with MTBE, then dried overnight over KOH pellets under high vacuum to provide the product (24.8 mg, 33 umol, 87%). LC/MS shows single peak having [M+H]⁺ = 698.2, calc. for C₃₂H₃₄ClFN₇O₈⁺ = 698.21.

**PEG-Conjugate 11A.** A solution of 4-arm PEG₄₀kDa-tetraamine (NOF America, 250 mg, 6.25 umol) in 2 mL of DMF was treated with a 24.8 mg/mL solution of 10A in DMF (800 μL, 26.4 umol, 1.06 Eq), N,N-diisopropylethylamine (10 μL, 60 umol, 2.4 Eq), and 100 mM HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) in DMF (300 μL, 30 umol, 1.2 Eq). HPLC analysis at 15 min indicated complete reaction. The mixture was dialyzed against 500 mL of 10 mM acetic acid using a SpectraPor2 membrane (10-12 kDa cutoff) for 2 hr, followed by methanol. The dialyzed material was evaporated to dryness, then dissolved in 5 mL of THF and precipitated by dropwise addition to 100 mL of stirred MTBE. The precipitate was collected by centrifugation, washed with MTBE, and dried under vacuum to give the conjugate as a waxy solid (220 mg, 82%). A 2.4 mg sample (55.9 umol based on MW = 42.9 kDa) was dissolved in 1000 μL of water for analysis. HPLC indicated a single peak, and the UV spectrum gave OD₃₀₃ = 1.4637, indicating 0.225 mM 4. This indicates a ratio of 4.02 moles of 4 per mole of 4-arm PEG. ¹H-NMR was consistent with the structure.

**PEG-conjugate 11B.** A solution of 4-arm PEG₄₀kDa-tetraamine (NOF America, 50 mg, 1.25 umol) and 10B (6.4 umol, 1.28 Eq) in 1 mL of DMF was treated with 100 mM N,N-diisopropylethylamine in DMF (128 μL, 12.8 umol, 10 Eq), and 100 mM HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) in DMF (130 μL, 13 umol, 1.2 Eq). HPLC analysis at 15 min indicated complete reaction. The mixture was dialyzed against 500 mL of 10 mM acetic acid using a SpectraPor2 membrane (10-12 kDa cutoff) for 2 hr, followed by methanol. The dialyzed material was evaporated to dryness, then dissolved in 5 mL of THF and precipitated by dropwise addition to 100 mL of stirred MTBE. The precipitate was collected by centrifugation, washed with MTBE, and dried under vacuum to give the conjugate as a waxy solid (220 mg, 82%). A 2.4 mg sample (55.9 umol based on MW = 42.9 kDa) was dissolved in 1000 μL of water for analysis. HPLC indicated a single peak, and the UV spectrum gave OD₃₀₃ = 1.4637, indicating 0.225 mM 4. This indicates a ratio of 4.02 moles of 4 per mole of 4-arm PEG. ¹H-NMR was consistent with the structure.

**PEG-conjugate 12.** A mixture of 4-arm PEG₄₀kDa-tetra(succinimidyl methyl ester) (JenKem Technologies, 250 mg, 6.25 umol) in 2 mL of DMF was treated with 4 (14.5 mg, 27.5 umol, 1.1 Eq), N,N-diisopropylethylamine (10 μL, 60 umol, 2.4 Eq), and 100 mM HATU (1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) in DMF (300 μL, 30 umol, 1.2 Eq). HPLC analysis at 30 min indicated complete reaction. The mixture was dialyzed against 500 mL of 10 mM acetic acid using a SpectraPor2 membrane (10-12 kDa cutoff) for 2 hr, followed by methanol. The dialyzed material was evaporated to dryness, then dissolved in 5 mL of THF and precipitated by dropwise addition to 100 mL of stirred MTBE.
The precipitate was collected by centrifugation, washed with MTBE, and dried under vacuum to give the conjugate as a waxy solid (180 mg, 70%). A 2.4 mg sample (55.9 umol based on MW = 42.9 kDa) was dissolved in 1000 μL of water for analysis. HPLC indicated a single peak, and the UV spectrum indicated a ratio of 3.6 moles of 4 per mole of 4-arm PEG.

II. Assays

**Human Factor D Assay.** Human factor D (R&D systems) at 1.25 ng/μl final concentration was incubated with 4 at various concentrations for 1 minute at room temperature in 92.5 μL 50 mM Tris, 1 M NaCl, pH 7.5. CFD substrate Z-L-Lys-SBzl (Bachem) and DTNB (Sigma-Aldrich) were added to final concentrations of 400 μM and 100 μM, respectively, in a final volume of 100 μL and reaction mixtures were incubated for 3 hr at ambient temperature. The increase in A405 was monitored in microplate spectrofluorimeter. IC50 values were calculated by non-linear regression from the % inhibition of CFD activity as a function concentration. Compound 4 showed a half-maximum inhibitory concentration (IC50) for CFD of 53 nM.

**Complement alternate pathway hemolytic assay.** Rabbit erythrocytes (Kooijin Bio) were washed in cold PBS and resuspended at 1 × 10⁹/mL in Veronal buffer (Lonza- from 5X VB) containing 0.1 % (w/v) Gelatin, 2.5 % (w/v) D-Glucose, 40 mM MgCl₂ and 10 mM EGTA (GVB buffer) in a total volume of 100 uL. Resuspended erythrocytes (3 × 10⁶ cells/well) were combined with 20% (final concentration) pooled complement human serum (Innovative Research) containing various dilutions of compound in GVB buffer (1% DMSO final concentration) and incubated for 1 hr at 37 °C; 0.1% Polyoxymethylene(10) Octylphenyl Ether (Wako) solution in GVB was used as the 100% lysis control and GVB containing 1% DMSO was used as the vehicle control. The reaction mixture was centrifuged and the supernatant was removed to a new plate. Optical density was measured at 415 nm and percent hemolysis was calculated as: (OD sample – OD vehicle)/(OD 100% lysis – OD vehicle) × 100%. Compound 4 showed a half-maximum inhibitory concentration (IC50) of AP-mediated hemolysis of 95 nM.

III. Pharmacokinetics of conjugates 11A, 12 and free 4.

**Dosing.** All animal procedures were performed in accordance with the in-house guidelines of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co., Ltd., and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Male Kbl:NZW rabbits (n = 6) were anesthetized using ketamine/xylazine and dosed in each eye with 5 μg (9.5 nmol) of free 4 in saline with 2% DMSO, 5 mg of conjugate 11A (465 nmol of 4) eye 5 mg of conjugate 12 (465 nmol of 4) in 50 μL of histidine buffer pH ~5.5 by IVT injection using 0.5 mL syringe with a 30 gauge needle. Regular feeding was resumed one hr after dosing with the exception of the 2-h sample group. Samples of the plasma, vitreous humor, retina, and choroid were obtained at 2 hr and then 1, 3, 7, 14, and 28 days post-injection of conjugates 11A and 12, and 0, 4 hr, 8 hr, 1 day, and 2 day post-injection of free 4 (n = 1 animal/point). Samples were immediately frozen on dry ice and stored at -60 °C until analysis. Mean concentrations of compounds in both eyes were used for pharmacokinetic analysis.

**Sample Analysis.** Rabbits were sacrificed with pentobarbital overdose (1.2 mL/kg). At death, both eyes were enucleated, and the vitreous was taken with a 1 mL syringe. Retinal tissues were separated into two layers - the neural retina (retina) and the retinal pigment epithelium / Bruch’s membrane /choriocaipillas (choroid). All samples were immediately frozen at ~80°C until tested. Frozen retina and choroid samples were thawed in a refrigerator (4°C) and 120 μL of distilled water was added to each retina or choroid sample, and samples were homogenized using a Shake Master NEO (Bio Medical Science K.K.) with tungsten beads (2.4 mm). For controls, retina
and choroid were obtained from an untreated rabbit. The dilution factor of retina and choroid tissue samples was calculated as \([0.12 + \text{tissue weight (g)})/\text{tissue weight (g)}}\).

**HPLC analysis of PEG conjugates 11A and 12.** Thirty μL of 50 μM citric acid and 60 μL of acetonitrile containing 50 μM citric acid were added to 30 μL of plasma, vitreous humour, choroid homogenate or retina homogenate. For calibration curves, 30 μL of 50 μM citric acid and 60 μL of acetonitrile containing 50 μM citric acid were added to 30 μL of each blank sample. After vortex mixing, samples were centrifuged (20,000 × g, 5 min, 4°C) and the supernatants analyzed by LC-UV. HPLC analysis used a Phenomenex Jupiter 5 um 300A C18 column, 4.6x150 mm (Shimadzu Corp.), thermostatted at 40 °C, with a flow rate of 1 mL/min and a gradient of 0-100% acetonitrile in water, both with 0.1% TFA. Samples were maintained at 4 °C in the autosampler and UV detection was at 301 nm. The LLOQ of 11A and 12 was 50 ng/mL.

**LC-MS/MS analysis of 4.** For the analytical samples from conjugates 11A and 12 administration, 20μL of 50 μM citric acid and 160 μL of 0.5 μM niflumic acid/50 μM citric acid in acetonitrile were added to 20 μL of plasma, vitreous humour, choroid homogenate or retina homogenate. For calibration curves, 20 μL of standard solution and 160 μL of 0.5 μM niflumic acid/50 μM citric acid in acetonitrile were added to 20 μL of each blank sample. For the analytical samples from free 4 administration, 20 μL of distilled water, 150 μL of acetonitrile, and 50 μL of acetonitrile containing 0.5 μM niflumic acid were added to 20 μL of vitreous humour. For calibration curves, 20 μL of distilled water, 50 μL of standard solution, 100 μL of acetonitrile, and 50 μL of acetonitrile containing 0.5 μM niflumic acid were added to 20 μL of blank vitreous humour. After vortex mixing, samples were filtered with Captiva (Agilent Technologies) prior to LC-MS/MS analysis. HPLC conditions used a Shimadzu Shim-Pack XR-ODS column, 2.1x30 mm thermostatted at 50 °C, with a flow rate of 0.75 mL/min. Buffer A was 50:950 (v/v) 0.1 M NH₄OAc/acetonitrile + 0.1% formic acid; buffer B was 50/900/50 (v/v/v) 0.1 M NH₄OAc/water/acetonitrile% + 0.1% formic acid, using a gradient from 50-100% B over 0.5 min. MS/MS spectra were obtained on a MDS Sciex API4000 in positive-ion mode, using MRM conditions of m/z 529.2 -> 268.9 for 4 and 283.0 -> 265.0 for niflumic acid. The LLOQ of 4 was 1- to 10 ng/mL.

**IV. Pharmacokinetic modeling.**

**Fig. S1** shows a two-compartment model used to analyze C vs t data for 11A and 4 after IVT injection of 11A.
Figure S1. Two-compartment vitreous ↔ periphery model for IVT PEG-4 conjugate 11A and released CFD inhibitor 4.

Table S1 shows parameters from a fit of the data to $C(t) = C_{\text{max}}[A \cdot e^{-at} + (1-A) \cdot e^{-bt}]$, with micro-constants derived according to standard methods. The values for $k_e$, $k_{12}$, and $k_{21}$ determined from IVT injection of 4 (text) and the corresponding parameters for the stable conjugate 12 were used in a numerical model for drug release to calculate the half-life for release rate of 4 from the releasable conjugate 11A in the vitreous.

Table S1. Two-compartment Fit for conjugates 11A and 12.

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<thead>
<tr>
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<th>$C_{\text{max}}$ ng/mL</th>
<th>A</th>
<th>A,d$^{-1}$</th>
<th>B,d$^{-1}$</th>
<th>$k_e$ d$^{-1}$</th>
<th>$k_{12}$ d$^{-1}$</th>
<th>$k_{21}$ d$^{-1}$</th>
<th>$t_{1/2}(b)$ d</th>
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<td>11A</td>
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A second noncompartmental pharmacokinetic analysis was performed using MathIQ on E-WorkBook Advance (ITCHU Techno-Solutions Corporation (CTC)), calculating area under the concentration-time curve (AUC), terminal rate constant ($\lambda_z$) and terminal half-life ($t_{1/2}$) for all compounds, steady-state volume of distribution ($V_{\text{ss}}$) and clearance (CL) for conjugates 11A and 12, and maximum concentration ($C_{\text{max}}$) for 4. Table S2 shows IVT pharmacokinetic parameters off 11A and 12, and Table S3 shows pharmacokinetic parameters for 4 released from 12A obtained by a non-compartmental fit. Table S3 shows the pharmacokinetic parameters for free 4 released from 11A using non-compartmental fitting.

Table S2. Pharmacokinetic parameters for conjugates 11A and 12 by non-compartmental fit

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<tr>
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<th>AUC d$\cdot\mu$g$\cdot$mL$^{-1}$</th>
<th>$V_{\text{ss}}$ mL</th>
<th>$CL_{\text{int}}$ mL$\cdot$d$^{-1}$</th>
<th>$I_z$ d$^{-1}$</th>
<th>$t_{1/2}$ d</th>
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Table S3. Pharmacokinetic parameters for 4 released from 11A

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<th>$C_{\text{max}}$</th>
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<th>$I_z$</th>
<th>$t_{1/2}$</th>
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<table>
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<th>(d^{-1})</th>
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