De novo Synthesis of Modified Saxitoxins for Sodium Ion Channel Study

Supplementary Information
(*14 pages*)

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General. All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of nitrogen. Air- and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated under reduced pressure (ca. 15 Torr) by rotary evaporation. Dichloromethane, tetrahydrofuran (THF) and acetonitrile (MeCN) were passed through two columns of activated alumina immediately prior to use. Pyridine was distilled from calcium hydride. *t*-Butyl-6-aminohexylcarbamate was prepared according to the procedure of Phanstiel.[1] Boron tris(trifluoroacetate) was prepared as described by Bauer as a 0.5 M solution in trifluoroacetic acid and stored in a Schlenk flask at –5 °C.[2] Chromatographic purification of products was accomplished using forced flow chromatography on Silicycle ultrapure silica gel (40–63 μm). Semi-preparative high performance liquid chromatography (HPLC) was performed on a Varian ProStar model 320. Thin layer chromatography was performed on EM Science silica gel 60 F_{254} plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with aqueous ceric ammonium molybdate (CAM) solution.

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Mercury spectrometer operating at 400 and 100 MHz for ^{1}H and ^{13}C, respectively, or on a Varian Inova spectrometer operating at 500 and 125 MHz for ^{1}H and ^{13}C, respectively, and are referenced internally according to residual solvent signals. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; quint, quintet; m, multiplet; br, broad), integration, coupling constant (Hz). Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded as thin films using NaCl plates on a Thermo-Nicolet 300 FT-IR spectrometer and are reported in frequency of absorption. High-resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

Cell culture and electrophysiology. Experiments were performed on Chinese hamster ovary cells (CHO) transfected with an expression vector containing the full-length cDNA coding for rat $Na_V1.4$ sodium channel α-subunit. Cells were transfected using the method of calcium phosphate precipitation; cotransfection with eGFP was used as a marker of transfection efficiency.

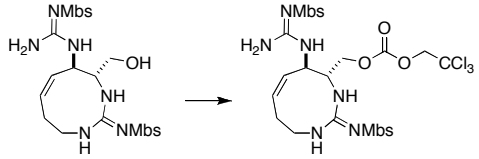
Sodium currents were measured using the patch-clamp technique in the whole-cell configuration with an Axopatch-200b amplifier (Axon Instruments, Union City, CA), as previously described by Moran.[3] Borosilicate glass micropipettes (Sutter Instruments, Novato, CA) were fire-polished to a tip diameter yielding a resistance of 1.0–2.0 MΩ in the working solutions. The pipette was filled with (in mM): NaF 40, EDTA 1, HEPES 20, CsCl 125, and the pH was adjusted to 7.4 with solid CsOH. The external solution had the following composition (in mM): NaCl 160, $CaCl_2$ 2, HEPES 20, and the pH was adjusted to 7.4 with solid CsOH. Current densities were generally between 2–4 nA.

Stock solutions of each of the toxin derivatives (NaCl 160 mM, $CaCl_2$ 2 mM, HEPES 20 mM; pH adjusted to 7.4 with solid CsOH) were maintained at 4 °C and diluted with external solution prior to recording. Current measurements were recorded under continuous perfusion, controlled manually by syringe addition. **Caution:** Saxitoxin derivatives are expected to show similar toxicity and symptomatology to saxitoxin, tetrodotoxin and other sodium channel blockers and should be handled with appropriate care for safety.

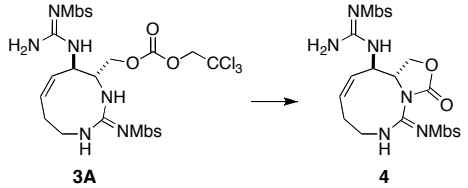
The output of the patch-clamp amplifier was filtered with a built-in low-pass, four-pole Bessel filter having a cutoff frequency of 10 kHz and sampled at 100 kHz. The membrane was kept at a holding potential of –100 mV. Pulse stimulation and data acquisition used 16 bit D-A and A-D converters (Axon Instruments Digidata 1322A) controlled with the PClamp software (Axon Instruments). Leak currents were subtracted using a standard P/4 protocol of the same polarity. Access resistance was always < 4 MΩ and the cell capacitance was between 4 and 20 pF, as measured by the compensating circuit of the amplifier. All measurements were done at room temperature (20–22

°C). Recordings were made at least 5 min after establishing the whole-cell and voltage-clamp configuration to allow for stabilization of the voltage-dependant properties of the channels. Currents were elicited by 10 ms step depolarizations from a holding potential of –100 to 0 mV. Data were normalized to control currents, plotted against toxin concentration and analyzed using custom software developed in the Igor environment (Wavemetrics). Data were fitted to Langmuir isotherms to elicit IC_{50} values and expressed as mean ± SE.

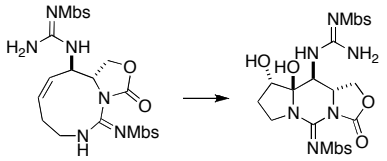
Experimental protocols and characterization data:



Trichloroethylchloroformate (49 μL, 0.35 mmol, 1.0 equiv) was added dropwise to an ice-cold solution of **3** (200 mg, 0.35 mmol) in 3.5 mL of pyridine. A gummy solid formed immediately which slowly dissolved. After stirring the mixture for 10 min, a second portion of trichloroethylchloroformate (49 μL, 0.35 mmol, 1.0 equiv) was added. The mixture was stirred for an additional 20 min at 0 °C. The reaction was then quenched by the addition of 10 mL of saturated aqueous $NaHCO_3$. The mixture was transferred to a separatory funnel with 10 mL of CH_2Cl_2. The organic phase was collected and the aqueous layer was extracted with 3 x 10 mL of CH_2Cl_2. The combined organic fractions were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a white solid. Chromatography on silica gel (94:6 CH_2Cl_2/MeOH) furnished **3A** as a white solid (244 mg, 93%): TLC R_f = 0.34 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz, 70 °C) δ 7.76-7.70 (m, 4H), 7.02-6.94 (m, 4H), 6.78 (br s, 1H), 6.16 (s, 2H), 5.62 (d, 1H, *J* = 7.0 Hz), 4.87 (d, 1H, *J* = 12.0 Hz), 4.82 (d, 1H, *J* = 12.0 Hz), 4.79 (m, 1H), 4.64 (br s, 1H), 4.61 (dd, 1H, *J* = 7.5, 7.5 Hz), 4.31 (dd, 1H, *J* = 18.0, 11.0 Hz), 4.28 (ddd, 1H, *J* = 11.5, 11.5, 3.5 Hz), 4.00-3.92 (m, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.48-3.34 (m, 2H), 2.74-2.64 (m, 1H), 2.19-2.12 (m, 1H) ppm; IR (thin film) ν 3333, 1764, 1597, 1531, 1499, 1255, 1131, 1081 cm^{-1}; HRMS (ES^+) calcd for $C_{26}H_{31}N_6O_9S_2$ 740.0481 found 763.0546 (MNa^+).



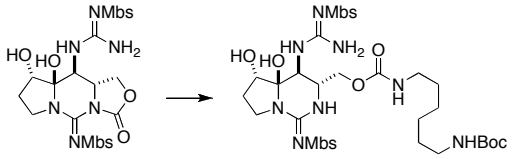
Diisopropylethylamine (535 μL, 3.1 mmol, 10 equiv) was added to a suspension of **3A** (228 mg, 0.31 mmol) in 6.0 mL of MeCN and the mixture was stirred at 60 °C for 12 h, during which time the solid material dissolved. The reaction was cooled to room temperature and concentrated under reduced pressure to give an off-white solid. The unpurified material was triturated with 5 mL of Et_2O and the off-white solids collected upon filtration to furnish **4** (156 mg, 86%): TLC R_f = 0.34 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.80 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.70 (dd, 2H, *J* = 7.0, 2.0 Hz), 7.04 (dd, 2H, *J* = 7.0, 2.0 Hz), 6.95 (dd, 2H, *J* = 7.0, 2.0 Hz), 6.25 (br s, 2H), 5.66 (br s, 1H), 4.73 (ddd, 1H, *J* = 14.5, 11.0, 5.0 Hz), 4.66 (br s, 1H), 4.61 (dd, 1H, *J* = 11.0, 7.5 Hz), 4.38 (dd, 1H, *J* = 8.0, 8.0 Hz), 4.22 (ddd, 1H, *J* = 10.0, 10.0, 1.5 Hz), 4.14 (dd, 1H, *J* = 9.0, 2.5 Hz), 3.85 (s, 3H), 3.82 (s, 3H), 3.61 (ddd, 1H, *J* = 14.5, 7.5, 3.0 Hz), 3.40 (m, 1H), 2.55-2.46 (m, 1H), 2.23-2.17 (m, 1H) ppm; IR (thin film) ν 3326, 3307, 1776, 1596, 1533, 1499, 1398, 1259, 1138, 1084 cm^{-1}; HRMS (ES^+) calcd for $C_{24}H_{28}N_6O_8S_2$ 592.1410 found 615.1308 (MNa^+).



4 **5**

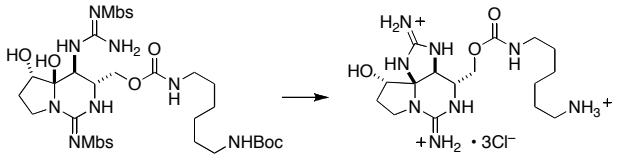
Oxone (436 mg, 0.71 mmol, 7.0 equiv) was added in a single portion to a mixture of $OsCl_3$ (36 mM solution in H_2O, 282 mL, 0.010 mmol, 0.10 equiv) and Na_2CO_3 (107 mg, 1.0 mmol, 10 equiv) in 4.3 mL of a 3:3:1 mixture of EtOAc/MeCN/H_2O. Mild gas evolution was observed and the resulting off-white mixture suspension was stirred for 2 min before oxazolidinone **4** (60 mg, 0.10 mmol) was added. The contents were stirred vigorously for 48 h. The reaction was then quenched by the addition of 5 mL of saturated $Na_2S_2O_3$ and the mixture was transferred to a separatory funnel containing 10 mL of H_2O and 20 mL of EtOAc. The organic layer was collected and the aqueous phase was extracted with 3 x 15 mL of EtOAc. The combined organic extracts were washed with 10 mL of saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. The solid residue was purified by chromatography on silica gel (92:8 CH_2Cl_2/MeOH) to give **5** as a white solid (28 mg, 44%): TLC R_f = 0.21 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz) δ 7.80-7.76 (m, 4H), 7.01-6.95 (m, 4H), 6.51 (br s, 2H), 6.07 (br s, 1H), 4.83 (br s, 1H), 4.46-4.40 (m, 2H), 4.32 (br s, 1H), 4.12 (d, 1H, *J* = 6.0 Hz), 3.92 (d, 1H, *J* = 3.5 Hz), 3.83 (s, 3H), 3.81 (s, 3H), 3.81-3.75 (m, 1H), 3.44 (ddd, 1H, *J* = 12.0, 12.0, 2.0 Hz), 2.25 (1H, signal obscured by DHO), 1.84 (dd, 1H, *J* = 12.5, 7.5 Hz) ppm; IR (thin film) ν 3326, 3307, 1776, 1596, 1533, 1499, 1398, 1259, 1138, 1084 cm^{-1}; HRMS (ES$^+$) calcd for $C_{24}H_{28}N_6O_{10}S_2$ 624.1308 found 625.1359 (MH^+).

A general three-step protocol was used to transform oxazolidinone **5** into STX derivatives **9**–**13**. Experimental details for the conversion of **5** to **11** are representative.



5 **6A**

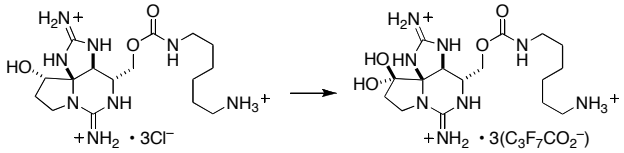
t-Butyl-6-aminohexylcarbamate (28 mg, 0.13 mmol, 5.0 equiv) was added to a solution of **5** (16 mg, 0.026 mmol) in 1.3 mL of THF. The mixture was stirred for 4 h, concentrated under reduced pressure and purified by chromatography on silica gel (94:6 CH_2Cl_2/MeOH) to give **6A** as a colorless oil (22 mg, 99%): TLC R_f = 0.30 (9:1 CH_2Cl_2/MeOH); ^{1}H NMR (CD_3CN, 500 MHz, 60 °C) δ 7.75 (dd, 4H, *J* = 9.0, 1.5 Hz), 6.98 (dd, 4H, *J* = 9.0, 2.5 Hz), 6.37 (br s, 2H), 5.81 (br s, 1H), 5.53 (br s, 1H), 5.11 (br s, 1H), 4.81 (br s, 1H), 4.29 (br d, 1H, *J* = 11.5 Hz), 4.13 (s, 1H), 4.03 (br t, 1H, *J* = 8.0 Hz), 3.94 (t, 1H, *J* = 3.5 Hz), 3.85 (s, 6H), 3.75 (dd, 1H, *J* = 12.0, 4.5 Hz), 3.67-3.63 (m, 1H), 3.58-3.50 (m, 2H), 3.07 (br s, 2H), 2.99 (ddd, 2H, *J* = 6.5, 6.5, 6.5 Hz), 2.23-2.16 (m, 1H), 1.85-1.81 (m, 1H), 1.51-1.40 (m, 4H), 1.42 (s, 9H), 1.34-1.25 (m, 4H) ppm; IR (thin film) ν 3330, 2932, 1701, 1578, 1535, 1499, 1256, 1132, 1082 cm^{-1}; HRMS (ES$^+$) calcd for $C_{35}H_{52}N_8O_{12}S_2$ 840.3146 found 863.3033 (MNa^+).



6A **7A**

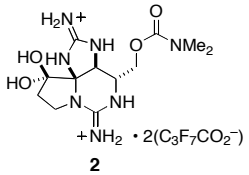
A 10 mL round bottom flask containing **6A** (23 mg, 0.027 mmol) was placed in an ice bath, and to it was slowly added $B(O_2CCF_3)_3$ (0.5 M solution in CF_3CO_2H, 1.64 mL, 0.82 mmol, 30 equiv). The resulting light brown solution

was stirred and slowly warmed to room temperature over 5 h. After stirring for an additional 14 h at this temperature, the solution was cooled to 0 °C, and the reaction quenched by the dropwise addition of 1.0 mL of MeOH. The mixture was concentrated under reduced pressure to an oily residue. The unpurified product was re-dissolved in ~2 mL of MeOH and the solution was concentrated. This process was repeated once. The isolated material was then dissolved in 1 mL of H_2O and passed through a 2 x 10 cm column of Dowex 1 x 8-200 ($^-$OH form). The fractions containing product, as determined by pH (>7.5), were collected and acidified with 100 μL of 1.0 M aqueous HCl. The solution was lyophilized to give **7A** as a white powder (12 mg, 92%): ^{1}H NMR (D_2O, 400 MHz) δ 4.77 (d, 1H, *J* = 1.2 Hz), 4.33 (d, 1H, *J* = 3.6 Hz), 4.26 (dd, 1H, *J* = 11.6, 9.2 Hz), 4.01 (dd, 1H, *J* = 11.6, 5.6 Hz), 3.81 (dd, 1H, *J* = 9.2, 5.6 Hz), 3.77 (ddd, 1H, *J* = 10.0, 10.0, 2.0 Hz), 3.67 (ddd, 1H, *J* = 18.8, 8.8, 1.6 Hz), 3.15-3.05 (m, 2H), 2.97 (dd, 2H, *J* = 7.6, 7.6 Hz), 2.46-2.36, (m, 1H), 2.23 (ddd, 1H, *J* = 14.8, 8.4, 1.6 Hz), 1.68-1.61 (m, 2H), 1.52-1.45 (m, 2H), 1.41-1.31 (m, 4H) ppm; HRMS (ES$^+$) calcd for $C_{16}H_{30}N_8O_3$ 382.2441 found 383.2514 (MH^+).

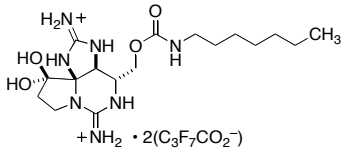


To a solution of **7A** (9 mg, 0.018 mmol) in 1.4 mL of DMSO was added powdered 3 Å molecular sieves. The suspension was stirred for 20 min prior to the addition of dicyclohexylcarbodiimide (45 mg, 0.22 mmol, 12 equiv) and pyridinium trifluoroacetate (27 mg, 0.14 mmol, 7.5 equiv). A white precipitate formed immediately; the slurry was stirred vigorously for 17 h. Lyophylization of the reaction mixture furnished a solid product that was suspended in 1 mL of H_2O and filtered through a short pad of Celite. An additional 2 x 1 mL of H_2O was used to ensure quantitative transfer of the material. The combined filtrates were lyophilized and the isolated solid was purified by reverse phase HPLC (Altima C18, 10 μm, 10 x 250 mm column, eluting with a gradient flow over 14 min of 20:80 MeCN/10 mM aqueous $C_3F_7CO_2H$ → 27:73 MeCN/10 mM aqueous $C_3F_7CO_2H$, 214 nm UV detection). At a flow rate of 6 mL/min, **11** had a retention time of 7.1 min and was isolated following lyophylization as a white powder (12 mg, 63%): ^{1}H NMR (D_2O, 500 MHz) δ 4.68 (s, 1H), 4.23 (dd, 1H, *J* = 11.5, 9.5 Hz), 3.97 (dd, 1H *J* = 11.5, 5.5 Hz), 3.78-3.74 (m, 2H), 3.52 (ddd, 1H, *J* = 18.5, 8.5, 1.5 Hz), 3.09-3.01 (m, 2H), 2.93 (dd, 2H, *J* = 6.4, 6.4 Hz), 2.38 (ddd, 1H, *J* = 14.0, 8.0, 2.0 Hz), 2.33-2.26 (m, 1H), 1.63-1.57 (m, 2H), 1.48-1.42 (m, 2H), 1.35-1.28 (m, 4H) ppm; HRMS (ES$^+$) calcd for $C_{16}H_{30}N_8O_4$ 398.2390 found 399.2472 (MH^+).

Note: When < 5 mg of a STX analogue was prepared, quantitative NMR was used to determine accurately the amount of sample. *t*-Butylalcohol was used as an internal standard, the delay time on the NMR spectrometer was set to 20 s, and the acquisition time was set to 10 s. A signal corresponding to the CH_3 groups in ^{t}BuOH (δ = 1.20 ppm, D_2O) appears in some of the attached spectra

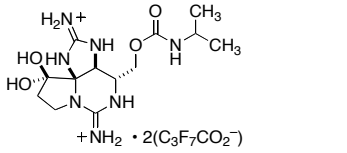


^{1}H NMR (D_2O, 500 MHz) δ 4.73 (d, 1H, *J* = 1.0 Hz), 4.29 (dd, 1H, *J* = 11.6, 9.5 Hz), 4.03 (dd, 1H, *J* = 11.6, 5.3 Hz), 3.84 (ddd, 1H, *J* = 9.3, 5.2, 0.9 Hz), 3.78 (ddd, 1H, *J* = 9.7, 9,7, 1.7 Hz), 3.55 (ddd, 1H, *J* = 9.7, 9.7, 8.2 Hz), 2.91 (s, 3H), 2.86 (s, 3H), 2.40 (ddd, 1H, *J* = 13.6, 7.8, 1.7 Hz), 2.32 (ddd, 1H, *J* = 13.7, 9.7, 9.7 Hz) ppm; HRMS (ES$^+$) calcd for $C_{12}H_{19}N_7O_3$ 309.1549 found 310.1633 (MH^+).



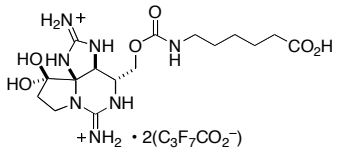
9

^{1}H NMR (D_2O, 400 MHz) δ 4.70 (s, 1H), 4.27 (dd, 1H, *J* = 11.6, 8.8 Hz), 3.99 (dd, 1H, *J* = 11.6, 5.2 Hz), 3.80-3.76 (m, 2H), 3.54 (dd, 1H, *J* = 7.6, 7.6 Hz), 3.11-3.04 (m, 2H), 2.39-2.30 (m, 2H), 1.45 (dd, 2H, *J* = 6.8, 6.8 Hz), 1.26-1.21 (m, 8H), 0.83 (t, 3H, *J* = 6.8 Hz) ppm; HRMS (ES^+) calcd for $C_{17}H_{31}N_7O_4$ 397.2438 found 398.2505 (MH^+).



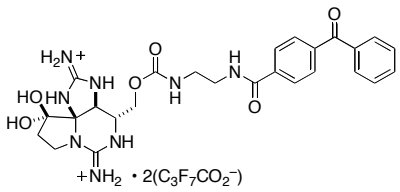
10

^{1}H NMR (D_2O, 500 MHz) δ 4.70 (s, 1H), 4.26 (dd, 1H, *J* = 11.5, 9.0 Hz), 3.99-3.95 (m, 1H), 3.80-3.75 (m, 2H), 3.66-3.60 (m, 1H), 3.54 (ddd, 1H, *J* = 18.0, 10.0, 1.5 Hz), 2.40 (ddd, 1H, *J* = 14.0, 8.0, 1.5 Hz), 2.34-2.28 (m, 1H), 1.09 (d, 6H, *J* = 7.0 Hz) ppm; HRMS (ES^+) calcd for $C_{13}H_{23}N_7O_4$ 341.1812 found 342.1890 (MH^+).



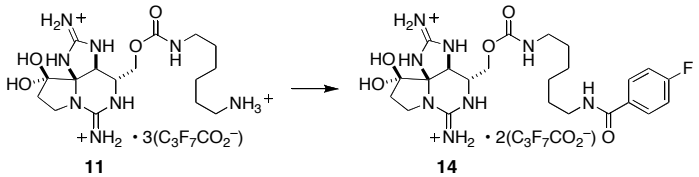
12

^{1}H NMR (D_2O, 500 MHz) δ 4.69 (d, 1H, *J* = 1.5 Hz), 4.27 (dd, 1H, *J* = 12.0, 9.5 Hz), 3.97 (dd, 1H, *J* = 11.5, 5.0 Hz), 3.78-3.71 (m, 2H), 3.52 (dd, 1H, *J* = 9.0, 9.0 Hz), 3.08 (dd, 2H, *J* = 6.5, 6.5 Hz), 2.15 (t, 2H, *J* = 7.0 Hz), 1.55-1.49 (m, 2H), 1.49-1.43 (m, 2H), 1.31-1.23 (m, 2H) ppm (note: ^{1}H signals for C11 methylene are absent due to exchange with D_2O); HRMS (ES^+) calcd for $C_{16}H_{27}N_7O_6$ 413.2023 found 414.2122 (MH^+).



13

^{1}H NMR (D_2O, 400 MHz) δ 7.87 (d, 2H, *J* = 9.2 Hz), 7.85 (d, 2H, *J* = 9.2 Hz), 7.81 (dd, 2H, *J* = 8.0, 1.2 Hz), 7.73 (tt, 1H, *J* = 7.6, 1.6 Hz), 7.57 (t, 2H, *J* = 8.0 Hz), 4.64 (d, 1H, *J* = 1.2 Hz), 4.17 (dd, 1H, *J* = 11.6, 9.6 Hz), 3.96 (dd, 1H, *J* = 11.6, 4.8 Hz), 3.74-3.69 (m, 2H), 3.53 (dd, 2H, *J* = 5.2, 5.2 Hz), 3.41-3.34 (m, 3H), 2.34-2.26 (m, 2H) ppm; HRMS (ES^+) calcd for $C_{26}H_{30}N_8O_6$ 550.2288 found 551.2388 (MH^+).



11 **14**

To a solution of **11** (2.5 mg, 2.4 μmol) in 240 μL of a 1:3 mixture of pH 9.5 buffer (0.1 M $NaHCO_3/Na_2CO_3$) and CH_3CN was added 4-fluorobenzoic acid *N*-hydroxysuccinimide ester (1.6 mg, 7.2 μmol, 3.0 equiv). The solution

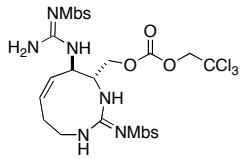
was stirred for 5 h, then acidified with 30 μL of 1.0 M aqueous HCl. The mixture was lyophilized to give a solid material that was purified by reverse phase HPLC (Altima C18, 10 μm, 10 x 250 mm column, eluting with a gradient flow over 30 min of 10:90 MeCN/10 mM aqueous $C_3F_7CO_2H$ → 40:60 MeCN/10 mM aqueous $C_3F_7CO_2H$, 254 nm UV detection). At a flow rate of 6 mL/min, **14** had a retention time of 16.2 min and was isolated following lyophylization as a white powder (2.2 mg, 96%): ^{1}H NMR (D_2O, 500 MHz) δ 7.75-7.72 (m, 2H), 7.21-7.18 (m, 2H), 4.68 (s, 1H), 4.21 (dd, 1H, *J* = 12.0, 9.5 Hz), 3.84 (dd, 1H, *J* = 12.0, 5.5 Hz), 3.78-3.74 (m, 2H), 3.54-3.49 (m, 1H), 3.34 (dd, 2H, *J* = 7.0, 7.0 Hz), 3.10-3.03 (m, 2H), 2.40-2.26 (m, 2H), 1.61-1.55 (m, 2H), 1.48-1.43 (m, 2H), 1.38-1.28 (m, 4H) ppm; HRMS (ES^+) calcd for $C_{23}H_{33}FN_8O_5$ 520.2558 found 521.2639 (MH^+).

(1) Gardner, R. A.; Ghobrial, G.; Nasser, S. A.; Phanstiel, O., IV *J. Med. Chem*. **2004**, *47*, 4933.

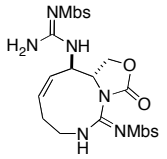
(2) Pless, J.; Bauer, W. *Angew. Chem. Int. Ed*. **1973**, *12*, 147.

(3) Moran, O.; Picollo, A.; Conti, F. *Biophys. J.* **2003**, *84*, 2999.

^{1}H NMR Spectral Data



(500 MHz, CD_3CN, 70 °C)



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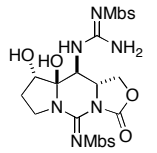

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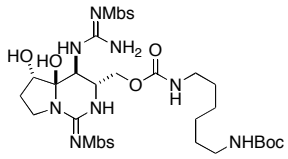
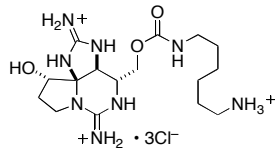
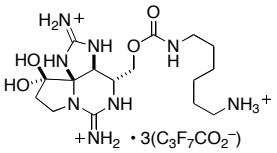


(500 MHz, CD_3CN, 60 °C)



(400 MHz, D_2O)



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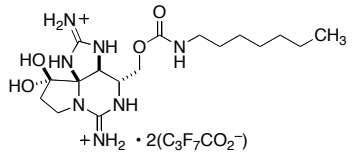

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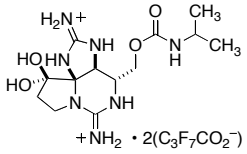

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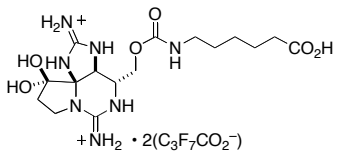

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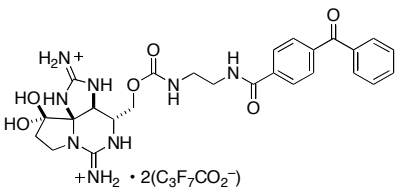
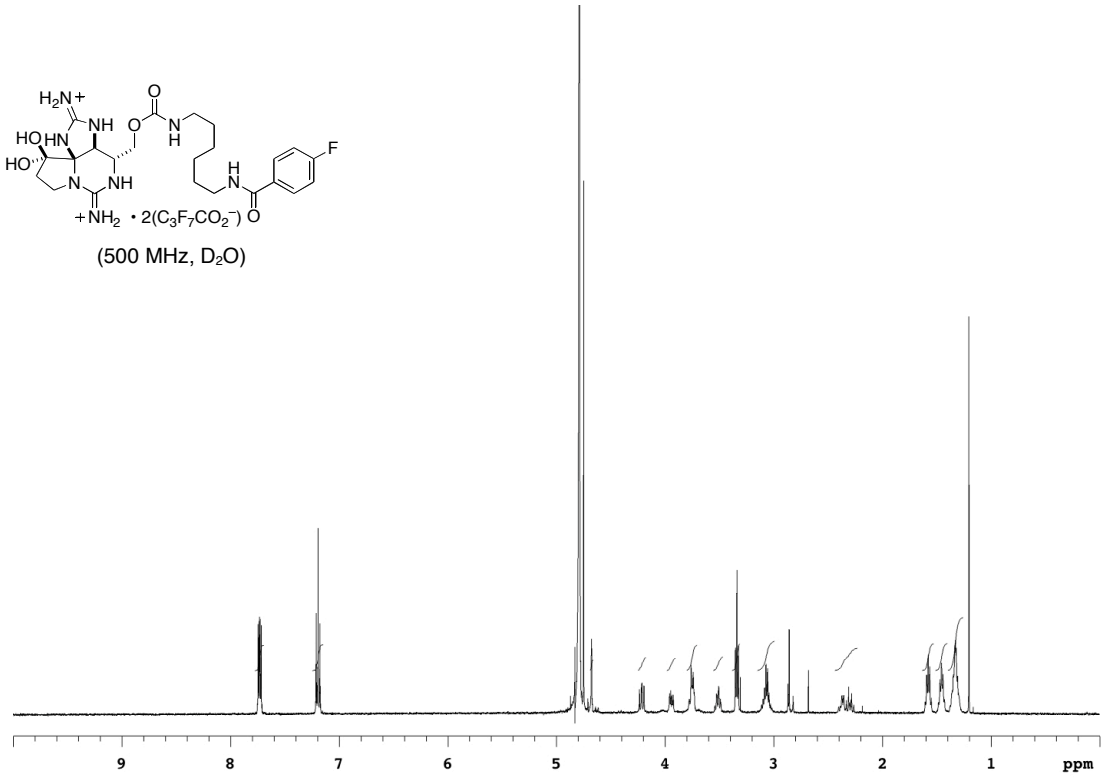


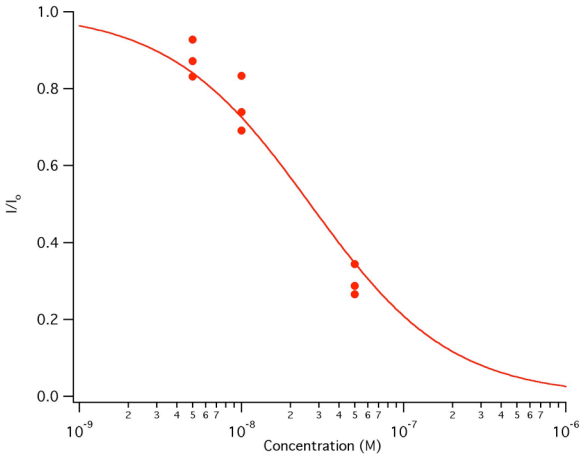
(400 MHz, D_2O)



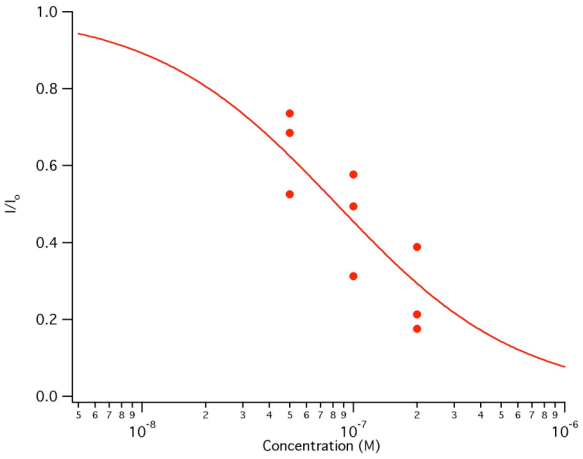
(500 MHz, D_2O)

Dose-response curves for STX derivatives against rNa$_V$1.4 (CHO cells)

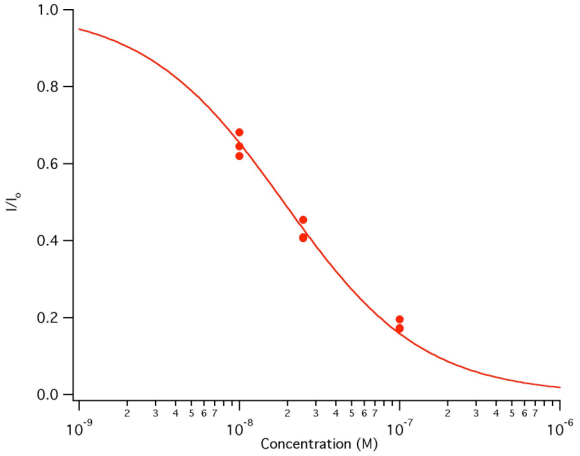
9 (*N*-heptyl)



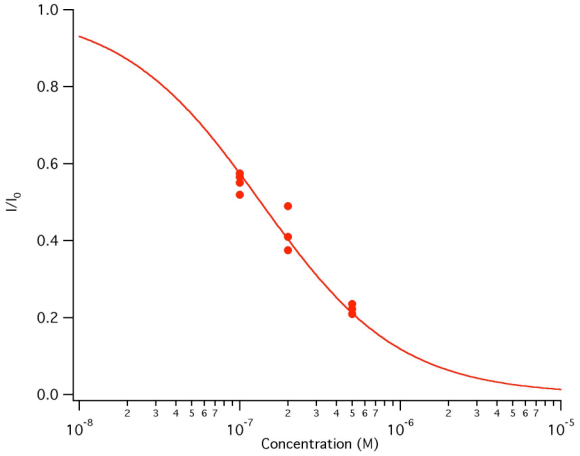
10 (*N*-isopropyl)



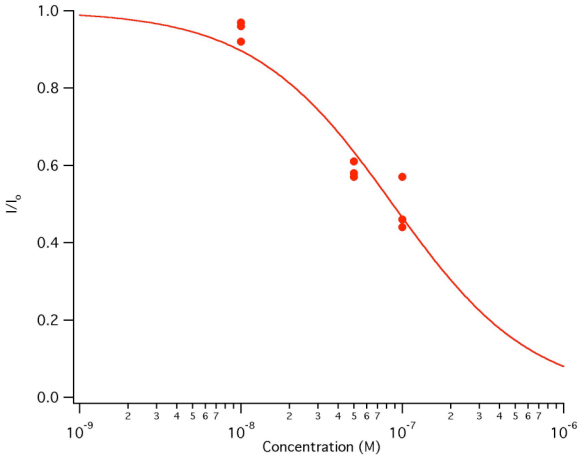
11 (*N*-hexylamine)



12 (*N*-hexanoic acid)



13 (*N*-ethyl benzophenone amide)



14 (*N*-hexyl-*p*-fluorobenzamide)