

Electronic Supplementary Information (ESI)

S1. DNA constructs and expression of Kv1 channels

cDNAs for rat Kv1.1, 1.2, 1.3, 1.4 and 1.6 were kindly provided by Professor Olaf Pongs (Institute for Neural Signal Transduction, University of Hamburg, Germany). HEK-293 cells (American Type Culture Collection) stably expressing Kv1.1, 1.2, 1.3, 1.4, or 1.6 were prepared as previously.¹

S2. Electrophysiological recordings and data analysis

Whole-cell voltage clamp was performed as before,² except where specified. In the conventional patch clamp system [EPC10 amplifier (HEKA Elektronik, Lambrecht/Pfalz, Germany)], the recording pipette was filled with an internal solution that contained (in mM): 95 KF, 30 KCl, 1 CaCl₂, 1 MgCl₂, 11 EGTA, 10 HEPES, 2 Na₂ATP (pH 7.2 with KOH), having fire-polished tips of resistances between 2-5 MΩ. Composition of the external (bath) medium (in mM) was: 135 NaCl, 5 KCl, 2 CaCl₂, 2 MgCl₂ and 5 Hepes, and 10 sucrose (pH 7.4 with NaOH). Correction was made for liquid junction potential (+7 mV). Leakage and capacitive currents were subtracted on-line using the P/4 subtraction protocol. Currents were filtered at 1 kHz, and sampled at 10 kHz. Only cells with a K⁺ current of >1 nA were chosen for experimentation, to avoid interference from endogenous outward currents (<200 pA at +20 mV potential), and having series resistances <10 MΩ throughout the experiments. Whole-cell currents were measured at a holding potential of -90 mV, and then depolarized to +20 mV for 300 ms. Currents from Kv channels being tested were calculated from averaged steady state values after 200 ms of activation. For Kv1.4, currents were determined from the averaged peak after activation. Time constants for activation (τ) were determined by fitting the I_K amplitudes corresponding to 40-90% of the maximum, at +20 mV, with a single exponential function.

Compounds were dissolved at 10 mM stocks in the extracellular solution and stored at -20 °C in amber tubes to prevent any photo-degradation. These were diluted in the extracellular solution in amber tubes to the desired concentrations before being superfused using Dynaflo-16 perfusion system (Celletricon, Mölndal, Sweden) or applied directly to the recording chamber (0.5 ml) at a flow rate of ~2ml/min. Dose-response curves were performed using Qpatch 16 automated machine (Sophion, Denmark), as reported previously.²

Electrophysiological results were re-plotted and fitted using Igor pro 6 (WaveMetrics, Lake Oswego, OR, USA) or Excel (Microsoft Ireland, Dublin, Ireland). Data are reported as mean \pm S.E.M.; *n* values refer to number of individual cells tested. Statistical significance was evaluated by an unpaired two-tailed Student's *t* test, using data obtained from at least three independent experiments. *P* values <0.05 were considered significant.

S3. Computational methods

The crystal structure of the mammalian Kv1.2 channel (PDB, 2A79,³) has previously been used as a template for building homology models of Kv1 homo-tetramers, and Kv1 hetero-tetramers.⁴⁻¹⁰ Protein structures were downloaded from the protein databank. Accelrys Discovery Studio 3.5 was used to prepare the protein structures. For ligands, tautomers, stereoisomers and conformations were enumerated using Accelrys Discovery Studio 3.5.

S4. Homology modelling

The protein sequences (for Kv1.1, 1.3, 1.4, and 1.6) were aligned to the template of the known structure (PDB: 2A79) using Discovery Studio 3.5 and 100 protein structures were built for each alignment. The Modeller software implemented comparative modelling of protein structure, by satisfying spatial restraints.^{11, 12} The alignment is used

to construct a set of geometrical criteria that are converted into probability density functions (PDFs) for each restraint. A global optimization procedure refines the positions of all heavy atoms in the protein. The best model was selected using a combination of the Modeller discrete optimized protein energy (DOPE) score and a selection of protein assessment tools. Profiles 3D (Accelrys Discovery Studio 3.5) checks the validity of a protein structure by measuring the compatibility score of each residue in the given 3D environment.¹³ PROCHECK¹⁴ was employed to perform a stereochemical check, with every amino acid being classified as having a favoured, additionally allowed, generously allowed, or disallowed conformation. ERRAT¹⁵ counts the number of non-bonded interactions between atoms (CC, CN, CO, NN, NO, and OO) within a cut-off distance of 3.5 Å and yields an overall quality factor for each structure, which is expressed as the % of protein for which the calculated error value falls below a 95% rejection limit. Normally accepted model structures produce values above 50, with a higher score indicating that the model has a better ratio of non-bonded interactions. Procheck and ERRAT validation were accessed at (<http://swift.cmbi.kun.nl/WIWWWI>). The final model selected yielded the overall best performance across the validation tools, coupled with a structural analysis of the binding pocket. Tetramer models were developed using Pymol¹⁶ and the biological assembly of the mammalian Shaker Kv1.2 channel (PDB: 2A79) structure.

S5. Molecular docking

The turret region was defined according to the residues highlighted in Figure 1 All atoms within 4 Å of these residues were selected and the combination was utilised to define a binding site sphere. The CDOCKER algorithm¹⁷ is a grid-based molecular docking method that employs CHARMm. The channel is held rigid while the ligands are allowed to flex during the refinement. Ligand placement in the active site is performed using a binding site sphere. Random ligand conformations are generated from the initial ligand structure through high temperature molecular dynamics, followed by random rotations. The random conformations are refined by grid-based (GRID 1) simulated annealing and a

final grid-based or full forcefield minimization. The docked ligands were minimized in the presence of the channel (*in situ*). Residues with atoms inside the specified sphere were allowed to move. In a subsequent flexible docking approach, a number of protein conformations were generated differing in side chain conformations in the turret region and the ligand poses rescored using the CDOCKER protocol.

S6. Autodock4 Flexible Docking

Ligands were allowed to be flexible (28 torsions for 12 (dd80) and 20 torsions for 10 (dd90)) and flexible residues for the protein were defined as residues 375-381 on each monomer. For each ligand all tautomer/stereoisomer variations were considered. A cubic grid of $100 \text{ \AA} \times 100 \text{ \AA} \times 100 \text{ \AA}$ around the active site was constructed using the Autogrid program, with a grid point step of 0.375 \AA .

A Lamarckian genetic algorithm, coupled with local search, was used for docking, with the default parameters implemented in Autodock4. The number of docking runs was set to 50, while `ga_num_evals` was set to 2,500,000 and `ga_num_generations` was set to 27,000. To generate input files, we used the AutoDockTools program. The conformations showing a lower free energy of binding for each ligand were further analyzed.

S7. Synthesis

Preparation of 5,10,15,20-tetrakis (4-carboxyphenyl) porphyrin (TCPP)

To a 250 mL round bottom flask, 1.5 g (10 mmol) of 4-formylbenzoic acid and 50 mL of propanoic acid were added and the reaction mixture was magnetically stirred. To increase the solubility of 4-formylbenzoic acid, the reaction mixture had to be heated to $80 \text{ }^{\circ}\text{C}$ at which point the aldehyde fully dissolved. Freshly distilled pyrrole (0.7 mL; 10 mmol) was added to the mixture, the temperature then brought to reflux and allowed to stir for 2 hrs at reflux. After allowing the reaction mixture to cool to room temperature, the reaction flask was placed in the freezer overnight to aid precipitation of the porphyrin. The reaction mixture was then vacuum filtered using a glass frit and a dark purple solid

collected, washed with 5x50 mL of DCM and dried overnight *in vacuo* to give 1.1g, of 5,10,15,20-tetrakis (4-carboxyphenyl) porphyrin (55% yield). ¹H NMR (600 MHz) δ (DMSO- d₆) 13.3 (4H, s, -COOH), 8.8 (8H, s, β -H), 8.3 (16H, dd, o+m phenyl H), -2.9 (2H, s, NH) ; ¹³C NMR (150 MHz) δ 167, 145, 134, 130, 127, 119. Mass Spec: (MALDI MS) Calculated (M) 790.2064, Observed (M+1) 791.0887. UV (EtOH): 418, 513, 546, 590 and 647 nm.

General procedure 1: Preparation of N-Boc protected porphyrins

To a 25 mL two necked round bottom flask, 235 mg (0.297 mmol) of TCPP was dissolved in 4 mL of anhydrous DMF. To this mixture was added 357 mg (1.96 mmol) of EDCI, 226 mg (1.96 mmol) NHS and the reaction mixture stirred at room temperature for 1 hr under nitrogen. After this time, a solution containing 376 μ L (2.36 mmol) of N-boc ethylenediamine and 295 mg (2.36 mmol) of DMAP both dissolved in 1 mL of anhydrous DMF was added drop-wise to the reaction mixture and allowed to stir for 24 hrs at room temperature. The mixture was then poured into 80 mL distilled H₂O and filtered through a glass frit. The resultant crude residue was subjected to column chromatography on silica gel and separated using a mobile phase of 90:10 DCM: ethanol to give the protected porphyrins.

Preparation of compounds 1-9

1. 5,10,15,20-tetrakis-2-([4-*tert*-butyl benzamido] ethyl carbamate) porphyrin.

General procedure 1 was followed using 235 mg (0.297 mmol) of TCPP and 376 μ L (2.36 mmol) of N-boc 1,2-diaminoethane. The isolated crude residue was subjected to column chromatography on silica and separated using a mobile phase 90:10 CH₂Cl₂: ethanol to give 282 mg of compound **1** (70% yield). ¹H NMR: (600MHz) δ (DMSO-d₆) 8.8 (12H, s, β -H+ NH Amide) 8.3 (16H, dd, J= 5.2 Hz, phenyl-H) 7.0 (4H, at, J=3.6 Hz, NH-Amide) 3.5 (8H, aq, J=3.6 Hz, CH₂) 3.3 (8H, aq, J=3.6 Hz) 1.4 (36H, s, Boc-H) -2.9 (2H, s, NH). ¹³C NMR (150 MHz): 166, 155, 143, 134.1, 134.05, 125.89, 119, 77, 39.5, 39.3, 28. Mass Spec: (MALDI MS) Calculated (M) 1358.6488; Observed (M+1) 1359.6915. UV (CH₂Cl₂): 420, 515, 549, 586 and 645 nm.

2. 5,10,15,20-tetrakis-3-([4-*tert*-butyl benzamido] propyl carbamate) porphyrin.

General procedure 1 was followed using 235 mg (0.297 mmol) of TCPP and 412 μ L; (2.36 mmol) of N-boc 1,3-diaminopropane. The isolated crude residue was subjected to silica gel column chromatography and separated using a mobile phase 90:10 DCM: ethanol, to give 286 mg of compound **2** (68% yield). ^1H NMR: (600MHz) δ (DMSO- d_6) 8.8 (12H, s, β -H+ NH Amide) 8.3 (16H, dd, J = 5.6 Hz, phenyl-H) 6.9 (4H, at, J = 4Hz, NH-Amide) 3.4 (8H, aq, J = 4Hz, CH_2) 3.1 (8H, aq, J = 4.4Hz, CH_2) 1.8 (8H, ap, J = 4.8 Hz, CH_2) 1.4 (36H, s, Boc-H) -2.9 (2H, s, NH). ^{13}C NMR (150 MHz) 166, 156, 143, 134, 125, 119, 77, 37.8, 37.1, 29.6, 28.2 Mass Spec: (MALDI MS) Calculated (M) 1414.7114, Observed (M+1) 1415.7576. UV: (DCM): 420, 515, 549, 586 and 645 nm.

3. 5,10,15,20-tetrakis-4-([4-*tert*-butyl benzamido] butyl carbamate) porphyrin.

General procedure 1 was followed using 235 mg (0.297 mmol) of TCPP and 452 μ L (2.36 mmol) of N-boc 1,4-diaminobutane. The crude residue was subjected to silica gel column chromatography and separated using a mobile phase 90:10 CH_2Cl_2 : ethanol, to give 286 mg of compound **3** (65% yield). ^1H NMR: (600MHz) δ (DMSO- d_6) 8.9 (12H, m, β -H+ NH Amide), 8.3 (16H, dd, J =5.6 Hz, phenyl-H) 6.9 (4H, aq, J =3.6 Hz, NH Amide) 3.4 (8H, aq, J = 4.4 Hz, CH_2) 3.1 (8H, aq, J = 4.4 Hz) 1.7 (8H, ap, J = 4.4 Hz, CH_2) 1.6 (8H, ap, J = 4.4 Hz, CH_2) 1.4 (36H, s, Boc-H) -2.9 (2H, s, NH) ^{13}C NMR (150 MHz) 166, 155, 143, 134.3, 134.1, 125, 119, 77, 39.8, 39.4, 28, 27, 26. Mass Spec: (MALDI MS) Calculated (M) 1470.7740, Observed (M+1) 1471.8192. UV: (DCM): 420, 515, 549, 586 and 645 nm.

4. 5,10,15,20-tetrakis-2-([4-*tert*-butyl benzamido] hexyl carbamate) porphyrin.

General procedure 1 was followed with 235 mg (0.297 mmol) of TCPP and N-boc 1,6-diaminohexane (530 μ L; 2.36 mmol). The collected crude residue was subjected to column chromatography on silica gel using a mobile phase of (20:1) methylene chloride: ethanol, to give 66 mg of compound **4** (14% yield). ^1H NMR: 8.8 (12H, m, β -H+ NH Amide), 8.3-8.2 (16H, dd, J =5.6, phenyl-H), 6.8 (4H, at, J =3.6Hz, NH Amide), 3.4 (8H, aq, J = 4Hz, CH_2), 2.9 (8H, aq, J =4Hz, CH_2), 1.6 (8H, ap, J = 4.8Hz, CH_2), 1.4 (24H, m, CH_2), 1.3 (36H, s, Boc-H), -2.9 (-2.9, s, NH) ^{13}C NMR (150 MHz) 166, 156, 144, 134.3, 134.1, 126, 119, 77, 39.7, 39.4, 30, 29, 28, 26.3, 26.1 Mass Spec: Calculated: (M)

1582.8992, Observed (M+1) 1182.97 (Boc cleaved, free NH₂ observed). UV (CH₂Cl₂): 420, 515, 549, 586 and 645 nm.

5. 5,10,15,20-tetrakis-2-([4-*tert*-butyl benzester] ethyl carbamate) porphyrin. To a two neck 25 mL round bottom flask was added TCPP (200 mg; 0.254 mmol) plus 4 mL of anhydrous DMF. The mixture was stirred under argon and cooled to 0°C on an ice bath. After stirring for 10 minutes at 0°C both EDCI (285 mg; 1.47 mmol) and DMAP (245 mg; 1.97 mmol dissolved in 1 mL of anhydrous DMF) were added simultaneously at 0°C. The mixture was stirred for 1 hr at 0°C, N-boc ethanolamine (320 µL; 2.04 mmol) was added dropwise and stirred for a further 30 mins at 0°C. The reaction was allowed to warm to room temperature and left to stir for 36 hrs before being poured into 80 mL of water and filtered. The collected precipitate was subjected to column chromatography using silica gel with 90:10 methylene chloride: ethanol as eluent and the isolate further purified by reprecipitation from a CHCl₃: hexane mixture (1:1), to give 277 mg of compound **5** (80% yield). ¹H NMR: (600MHz) δ (CDCl₃) 8.8 (8H, s, β-H) 8.5 (8H, d, phenyl-H) 8.3 (8H, d, phenyl-H) 5.0 (4H, t, NH-carbamate) 4.6 (8H, t, CH₂) 3.7 (8H, q, CH₂) 1.5 (36H, s, Boc-H) -2.8 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M) 1362.5849, Observed (M+1) 1363.6461.

6. 5,10,15,20-tetrakis-2-([*tert*-butyl-(2-benzamidoethyl) (2-((*tert*-butoxycarbonyl) amino) ethyl) carbamate porphyrin. General procedure 1 was used with 250 mg (0.313 mmol) of TCPP and *tert*-butyl (2-aminoethyl)(2-((*tert*-butoxycarbonyl) amino) ethyl) carbamate (0.76 g; 2.5 mmol). The collected precipitate was subjected to column chromatography on silica gel with 95:5 methylene chloride: ethanol as eluent, to give 212 mg of compound **6** (35% yield). ¹H NMR: (600MHz) δ (DMSO-d₆) 8.9 (12H, m, β-H+ NH amide) 8.3 (16H, m, phenyl-H) 7.0 (4H, m, NH-amide) 3.5 (16H, m, CH₂) 3.3 (8H, m, CH₂) 3.1 (8H, m, CH₂) 1.4 (72H, d, Boc-H) -2.9 (2H, s, NH).

7. 5,10,15,20-tetrakis 2-([di-*tert*-butyl ((benzoylazediy)bis(ethane-2,1-diyl))dicarbamate porphyrin. General procedure 1 was followed using TCPP (250 mg; 0.313 mmol) and di-*tert*-butyl (azanediy)bis(ethane-2,1-diyl))dicarbamate (0.76 g; 2.5 mmol) to give 399 mg of compound **7** (66% yield). ¹H NMR: (600MHz) δ (DMSO-d₆)

8.9 (8H, s, β -H) 8.3 (8H, d, phenyl-H) 7.8(8H, d, phenyl-H) 7.1 (8H, m, NH-amide) 3.6 (16H, m, CH₂) 3.3 (8H, m, CH₂) 3.2 (8H, m, CH₂) 1.4 (72H, d, Boc-H) -2.9 (2H, s, NH).

8. General procedure 2: N-(2-(dimethylamino)ethyl)benzamide porphyrin

TCPP (500 mg; 0.632 mmol) was charged into a 25 mL two neck round bottom flask, 10 mL anhydrous DMF added, the reaction mixture placed on an ice-bath and allowed to stir under argon for 15 minutes. To this mixture both EDCI (740 mg; 3.86 mmol) and NHS (340 mg; 3.86 mmol) were added and the mixture stirred at 0°C for a further hr. N,N dimethylethylenediamine (552 μ L; 4.38 mmol) was added at 0°C and the reaction allowed to stir at 0°C for a further 20 minutes. After warming to room temperature, the mixture was stirred overnight, poured into 80 mL of water and filtered. The precipitate was collected and subjected to column chromatography using silica gel and a mobile phase of 5:5:1 CHCl₃: EtOH : NH₃OH. The collected product was further purified by reprecipitation from MeOH/H₂O (1:1) to give compound **8** (62% yield). ¹H NMR: (600MHz) δ (CDCl₃) 8.8 (8H, s, β -H) 8.3 (8H, dd, J=5.2Hz, phenyl-H) 8.2 (8H, dd, J=5.2Hz, phenyl-H) 7.3 (4H, at, J=3.2Hz, NH Amide), 3.7 (8H, aq, J=3.6Hz, CH₂), 2.6 (8H, at, J=3.6Hz, CH₂) 2.3 (24H, s, N-CH₃) -2.8 (2H, s, NH) ¹³C NMR (150 MHz) 168, 145, 134.6, 134.2, 126, 119, 58, 45, 34. UV (CH₂Cl₂): 418 nm, 513 nm, 546 nm, 590 nm, 647 nm. Mass Spec: (MALDI MS) Calculated (M) 1070.5643, Observed (M+1) 1071.5953.

9. 5,10,15,20-tetrakis N-(3-(dimethylamino)propyl)benzamide porphyrin. General procedure 2 was followed using TCPP (500 mg; 0.632 mmol) and N,N dimethylpropylenediamine (552 μ L; 4.38 mmol) to give 413 mg of compound **9** after purification (59% yield). ¹H NMR: (600MHz) δ (CDCl₃) 8.9 (4H, at, J= 3.2Hz, NH Amide) 8.8 (8H, s, β -H) 8.2 (8H, dd, J=5.2Hz, phenyl-H) 8.1 (8H, dd, J= 5.2, phenyl-H) 3.7 (8H, aq, J= 3.6Hz, CH₂) 2.6 (8H, at, J=4Hz, CH₂) 1.9 (8H, ap, J=4Hz, CH₂) -2.8 (2H, s, NH) ¹³C NMR (150 MHz) 167, 145, 135, 134, 125, 119, 60, 46, 41, 25. UV (CH₂Cl₂): 418 nm, 513 nm, 546 nm, 590 nm, 647 nm. Mass Spec: (MALDI MS) Calculated (M) 1126.6269, Observed (M+1) 1127.6917.

General procedure 3: Deprotection of N-boc protected porphyrins.

To a 25 mL round bottom flask, 80 mg of boc protected porphyrin was added and placed over argon. Anhydrous CH_2Cl_2 (5 mL) was added and the mixture stirred at 0°C for 15 mins before the dropwise addition of 1mL of 4M HCl in dioxan (the reaction mixture was kept at 0°C during the addition). The reaction was stirred overnight at room temperature, before being poured into 30 mL diethyl ether and the precipitate collected by suction filtration. The precipitate was washed with two 10 mL aliquots of diethyl ether. Procedure 3 was employed with 80 mg of each starting material to prepare compounds 10-17.

10. 5,10,15,20-tetrakis 2-([4-*tert*-butyl benzamido] ethyl carbamate) porphyrin was used and the product isolated as a green solid in quantitative yield. ^1H NMR: (600MHz) δ (DMSO- d_6) 9.2 (4H, t, NH-amide) 8.8 (8H, s, β -H) 8.4 (16H, dd, phenyl-H) 8.2 (12H, s, NH_3) 3.7(8H, q, CH_2) 3.1 (8H, q, CH_2) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 958.4391, Observed (M+1-4HCl) 959.4461. (as per reference 18)

11. 5,10,15,20-tetrakis 3-([4-*tert*-butyl benzamido] propyl carbamate) porphyrin was used and the product isolated as a green solid in quantitative yield. ^1H NMR: (600MHz) δ (DMSO- d_6) 9.1 (4H, t, NH-amide) 8.9 (8H, s, β -H) 8.4 (16H, s, phenyl-H) 8.0 (12H, s, NH_3) 3.5(8H, t, CH_2) 3.0 (8H, q, CH_2) 2.0 (8H, p, CH_2) -2.9 (2H, s, NH) Mass Spec: (MALDI MS) Calculated (M-4HCl) 1014.5017, Observed (M+1-4HCl) 1015.5107. (as per reference 18)

12. 5,10,15,20-tetrakis 4-([4-*tert*-butyl benzamido] propyl carbamate) porphyrin was used and the product isolated as a green solid in quantitative yield. ^1H NMR: (600MHz) δ (DMSO- d_6) 9.0 (4H, t, NH-amide) 8.8 (8H, s, β -H) 8.3 (16H, s, phenyl-H) 7.9 (12H, s, NH_3) 3.5(8H, under water peak, CH_2) 2.9 (8H, m, CH_2) 1.7 (16H, m, CH_2) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 1070.5643, Observed (M+1-4HCl) 1071.5763. (as per referece 18)

13. 5,10,15,20-tetrakis 6-([4-*tert*-butyl benzamido] hexyl carbamate) porphyrin was used to give a green solid in quantitative yield. ^1H NMR: (600MHz) δ (DMSO- d_6) 9.0 (4H, t,

NH-amide) 8.9 (8H, s, β -H) 8.3 (16H, s, phenyl-H) 8.0 (12H, s, NH₃) 3.5 (8H, q, CH₂) 2.8 (8H, q, CH₂) 1.7 (16H, m, CH₂) 1.4 (16H, m, CH₂) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 1182.6895, Observed (M+1-4HCl) 1183.7438.

14. 5,10,15,20-tetrakis 2-([4-*tert*-butyl benzester] ethyl carbamate) porphyrin was used to give a green solid in quantitative yield. ¹H NMR: (600MHz) δ (DMSO-d₆) 8.9 (8H, s, β -H) 8.6 (8H, d, phenyl-H) 8.4 (8H, d, phenyl-H) 8.37 (12H, s, NH₃) 4.6 (8H, q, CH₂) 3.4 (8H, q, CH₂) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 962.3752, Observed (M+1-4HCl) 963.3757.

15. 5,10,15,20-tetrakis 2-([di-*tert*-butyl ((benzoylzanediyl)bis(ethane-2,1-diyl))dicarbamate porphyrin was used to produce a green solid in quantitative yield. ¹H NMR: (600MHz) δ (DMSO-d₆) 9.6 (8H, s, NH₂) 9.2 (4H, t, NH-amide) 8.8 (8H, s, β -H) 8.4 (20H, m, phenyl-H+NH₃) 8.3 (8H, d, phenyl-H) 3.8 (8H, m, CH₂) 3.4 (16H, m, CH₂) 3.3 (8H, m, CH₂) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 1130.6079, Observed (M+1-4HCl) 1131.5670.

16. 5,10,15,20-tetrakis-2-([*tert*-butyl-(2-benzamidoethyl) (2-((*tert*-butoxycarbonyl) amino) ethyl) carbamate porphyrin was used to produce a green solid in quantitative yield. ¹H NMR: (600MHz) δ (DMSO-d₆) 9.1 (8H, s, β -H) 8.4 (12H, s, NH₃) 8.27 (8H, d, phenyl-H) 8.1 (8H, s, NH₂) 8.0 (8H, d, phenyl-H) 3.9 (16H, m, CH₂) 3.2 (16H, m, CH₂) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 1130.6079, Observed (M+1-4HCl) 1131.6693.

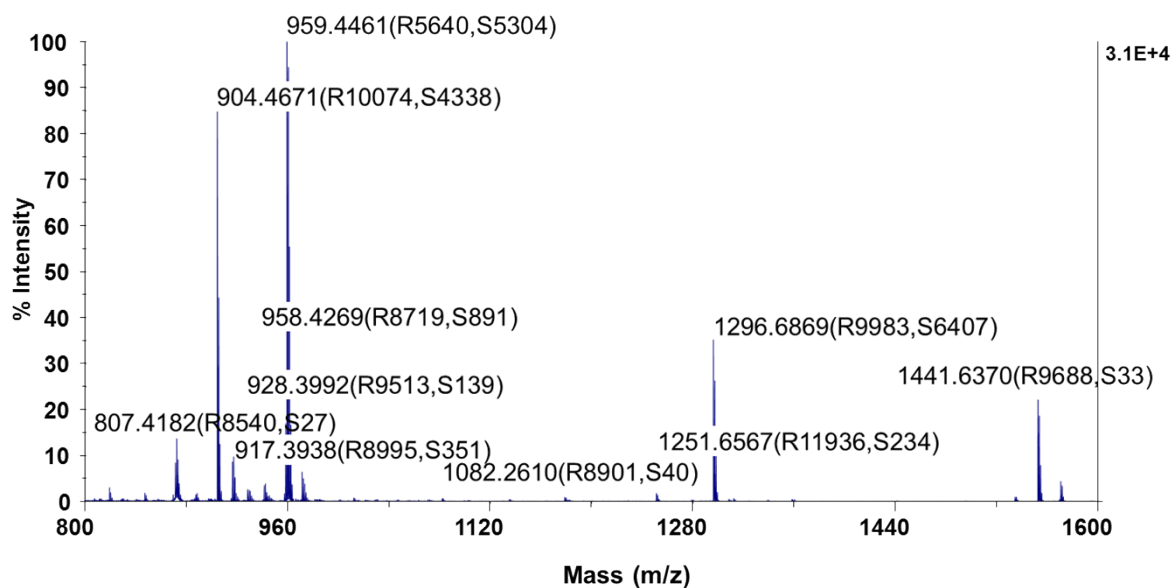
17. The preparation procedure used 5,10,15,20-tetrakis N-(2-(dimethylamino)ethyl)benzamide porphyrin to give a green solid in quantitative yield. ¹H NMR: (600MHz) δ (DMSO-d₆) 8.3 (4H, s, NH(CH₃)₂) 9.3 (4H, t, NH-amide) 8.5 (8H, s, β -H) 8.4 (16H, s, phenyl-H) 3.8 (8H, m, CH₂) 3.4 (8H, m, CH₂) 2.9 (24H, d, (CH₃)₂) -2.9 (2H, s, NH). Mass Spec: (MALDI MS) Calculated (M-4HCl) 1070.5643, Observed (M+1-4HCl) 1071.5973. (as per reference 19)

18. Use of 5,10,15,20-tetrakis N-(3-(dimethylamino)propyl)benzamide porphyrin gave a green solid in quantitative yield. ¹H NMR: (600MHz) δ (DMSO-d₆) 8.0 (4H, s, NH(CH₃)₂) 9.1 (4H, t, NH-amide) 8.8 (8H, s, β-H) 8.3 (16H, s, phenyl-H) 3.5 (8H, m, CH₂) 3.2 (8H, m, CH₂) 2.8 (24H, d, (CH₃)₂) 2.1 (8H, p, CH₂) -2.9 (2H, s, NH). Exact mass: 4.HCl: 1270.5336 Mass Spec: (MALDI MS) Calculated (M) 1126.6269, Observed (M+1) 1127.6328. (as per reference 19)

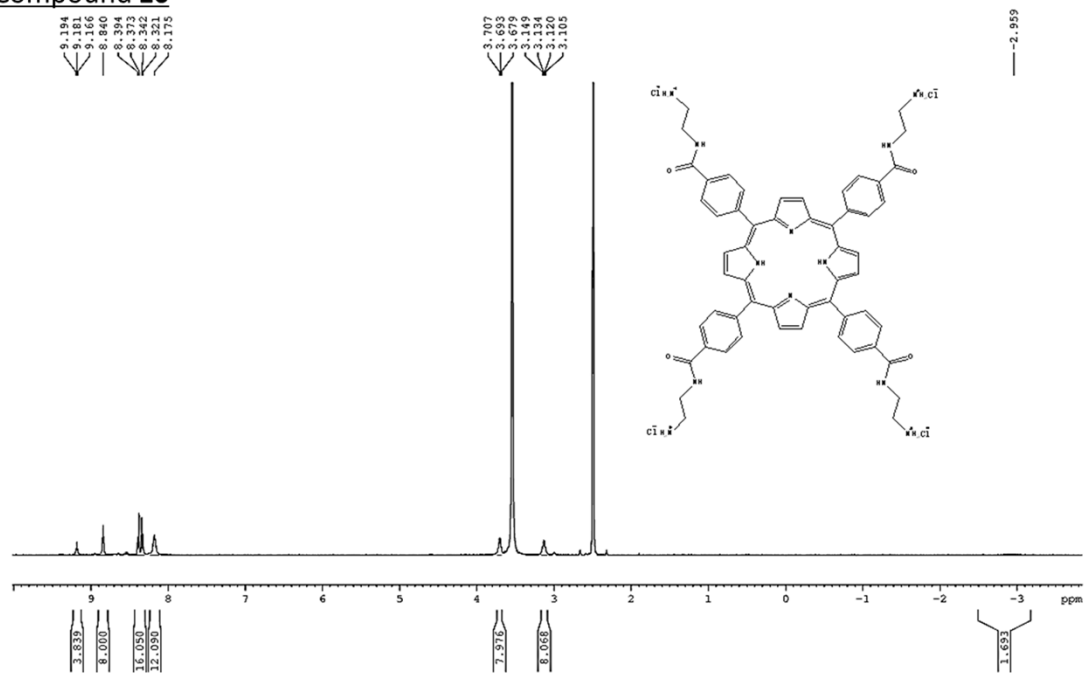
S8. MS and ^1H NMR spectra for compounds **10-18**

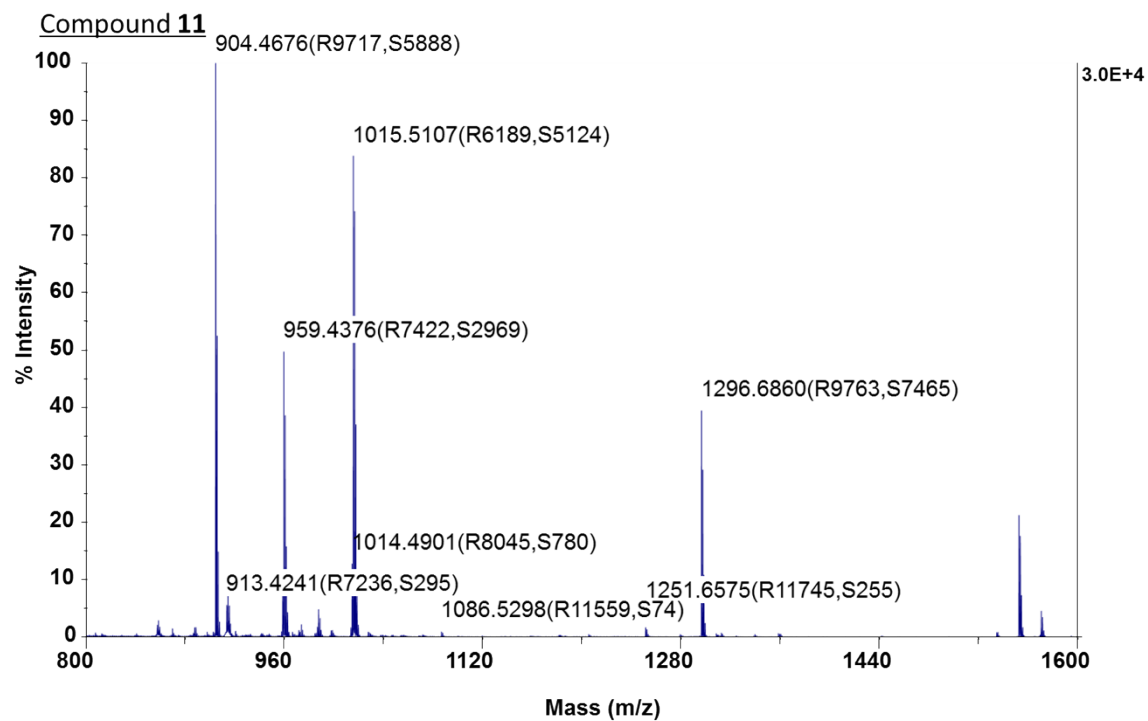
Internal calibrants (904.467 and 1296.686)

Compound 10

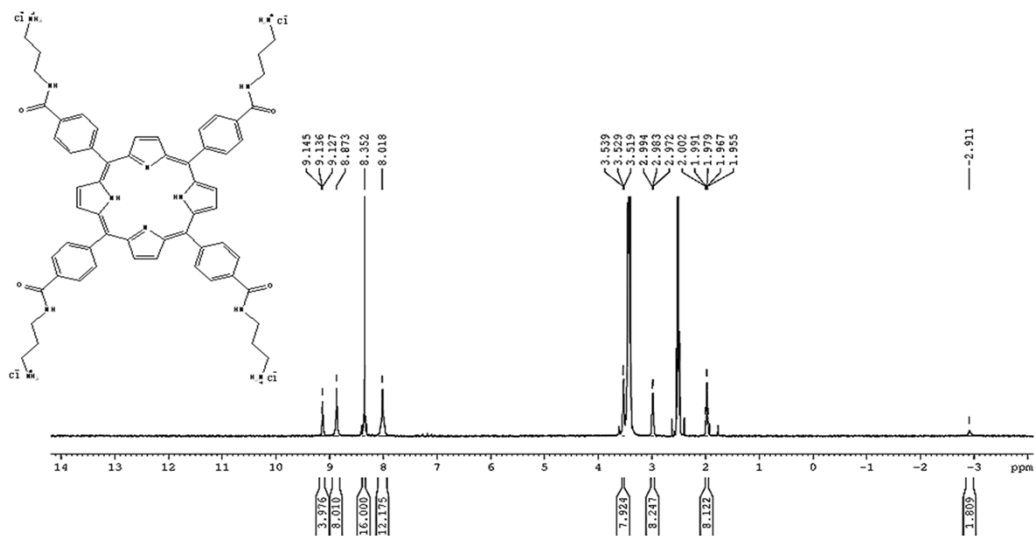


Compound 10

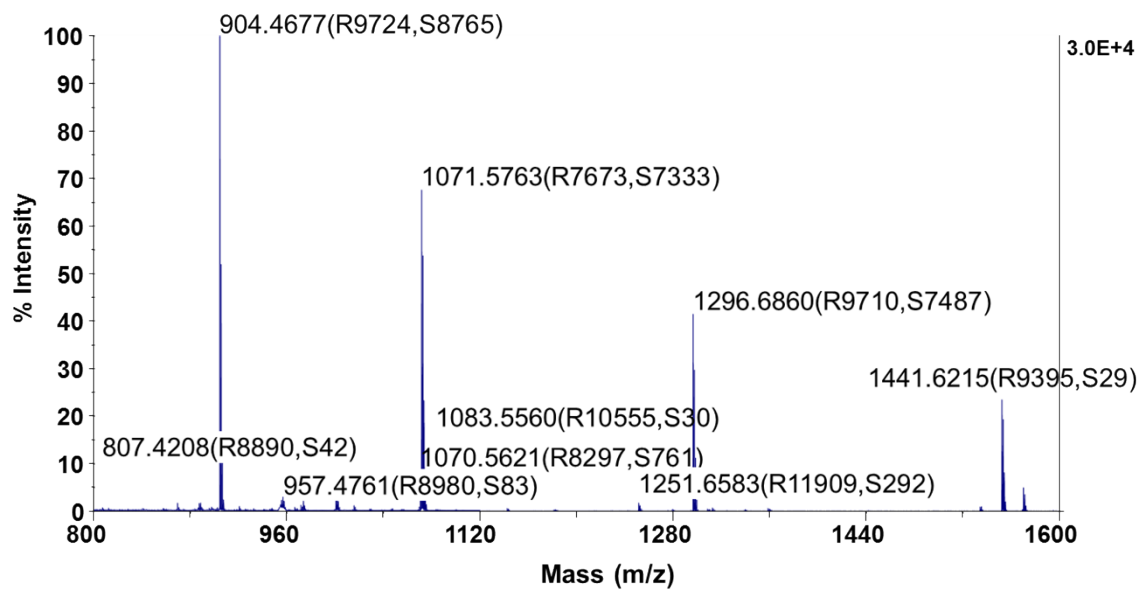




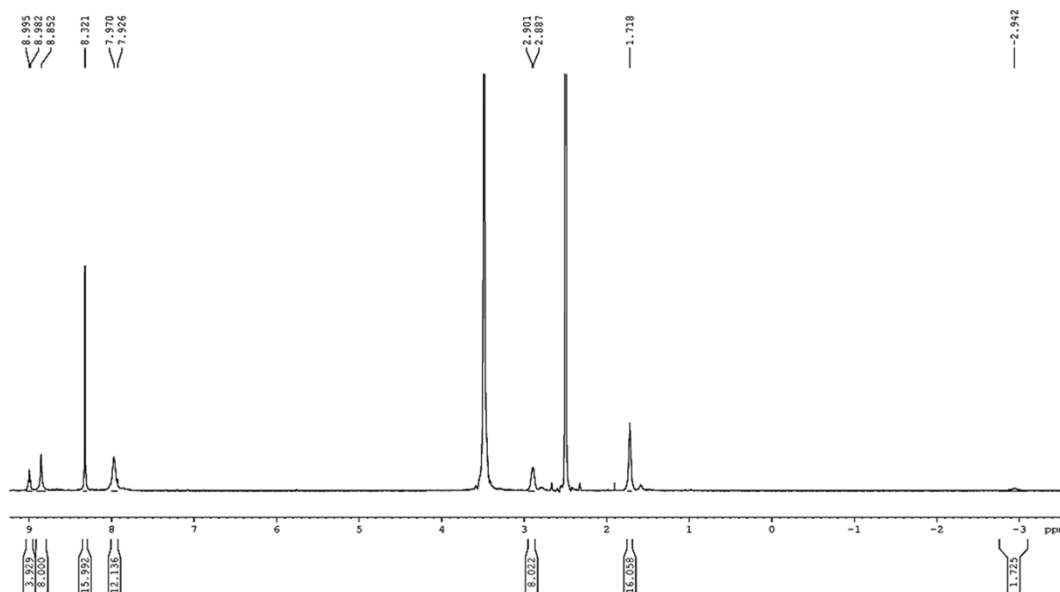
Compound 11



Compound 12

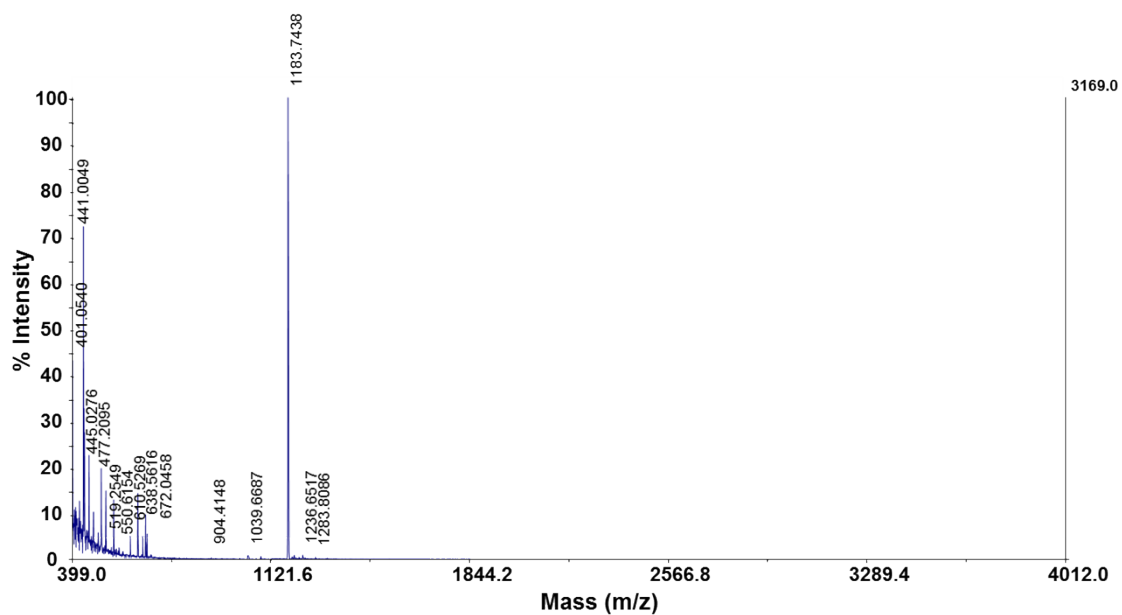


Compound 12

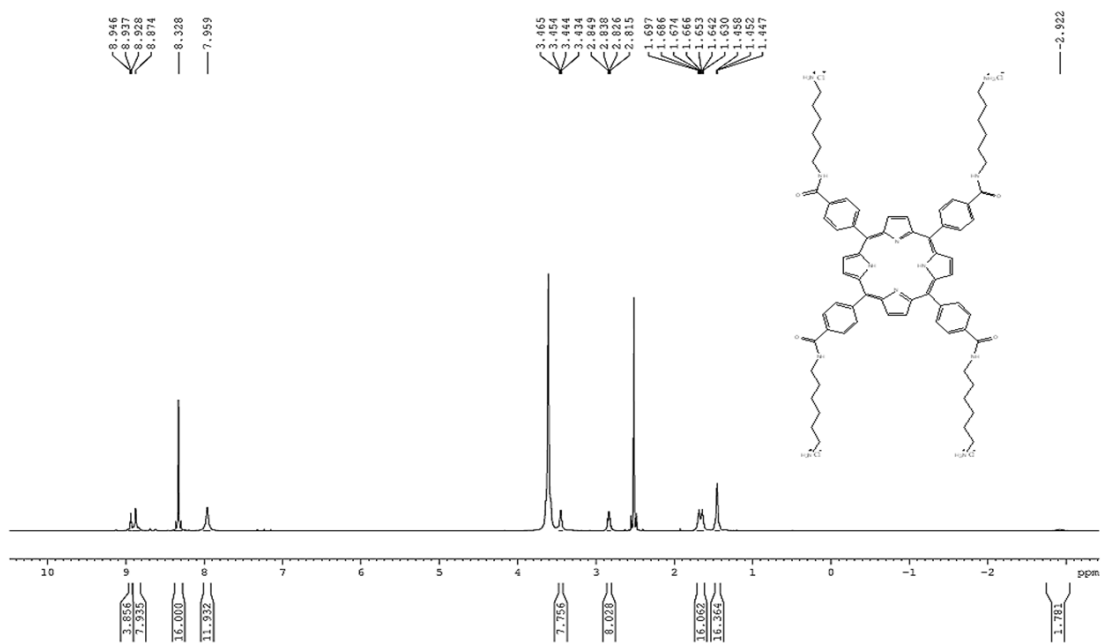


Note: One CH₂ masked under H₂O peak from the hydroscopic DMSO-d₆

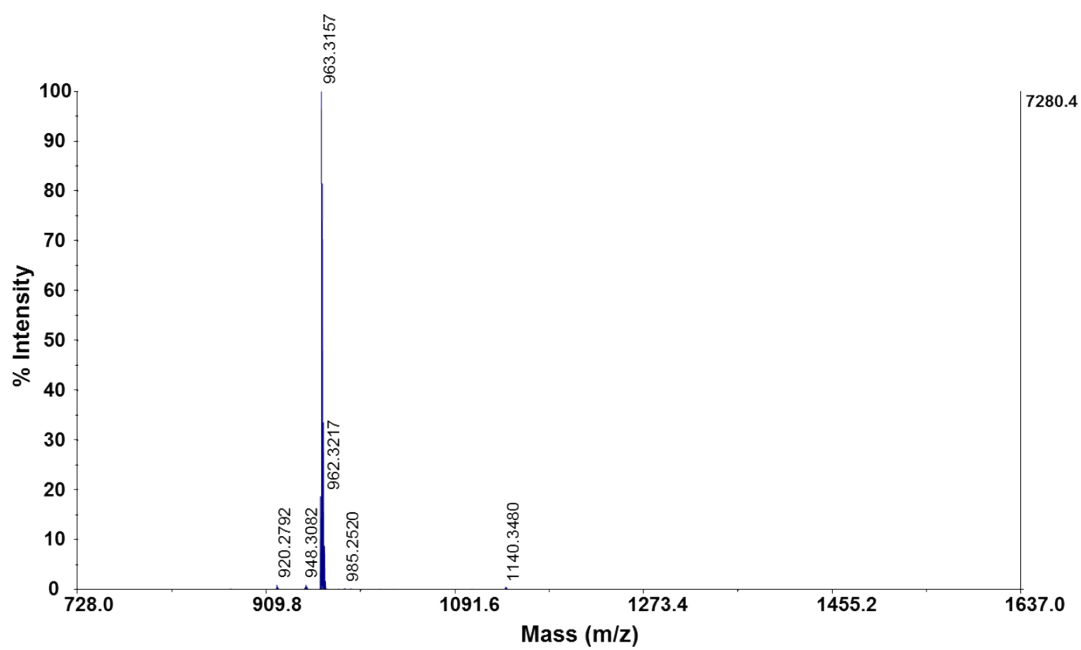
Compound 13



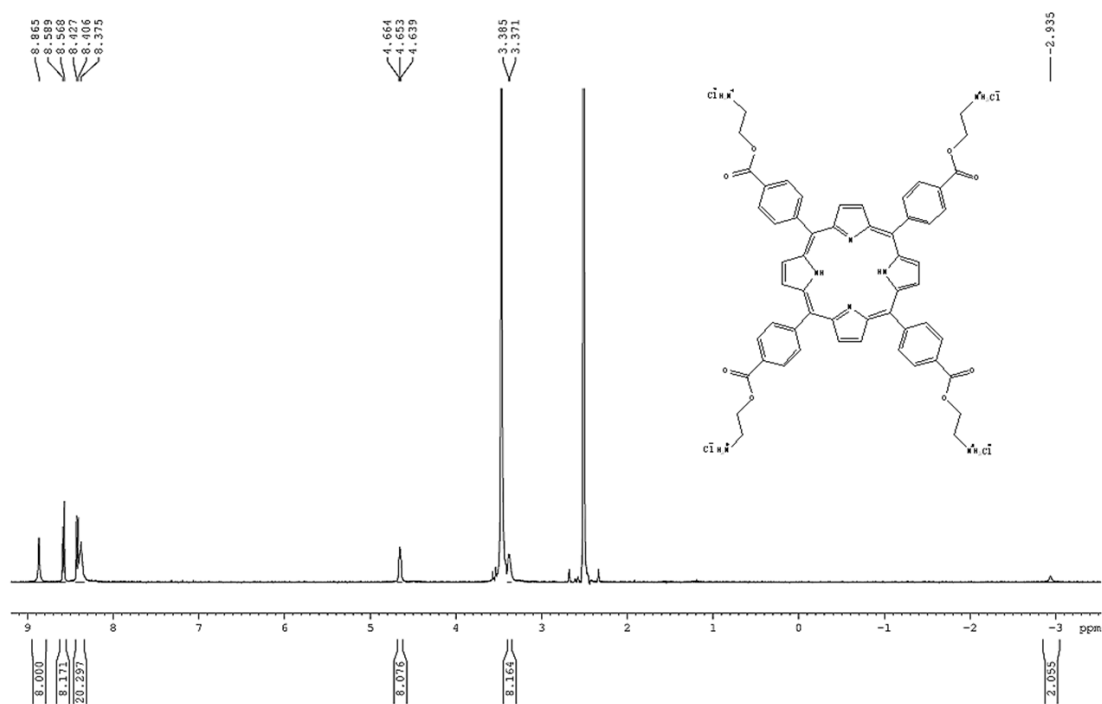
Compound 13



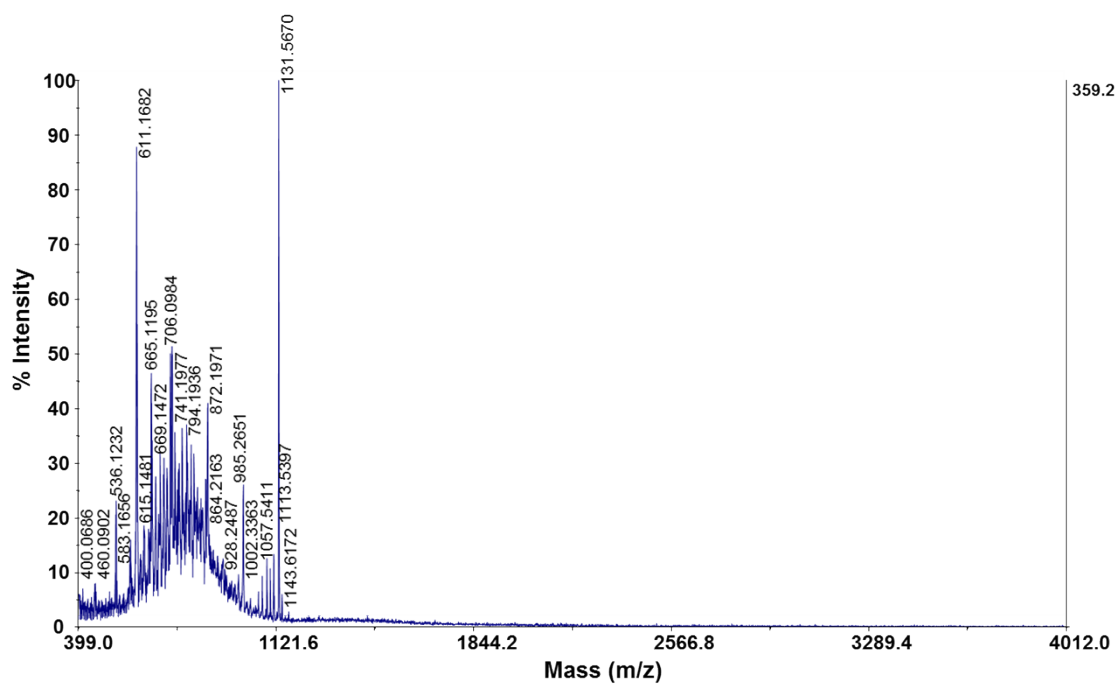
Compound 14



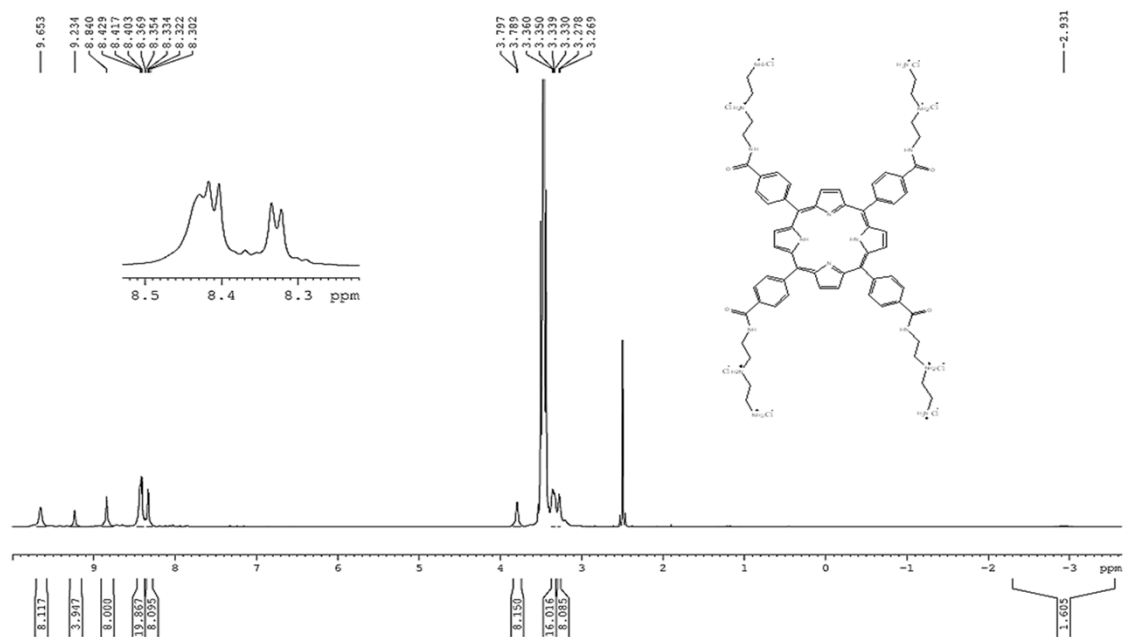
Compound 14



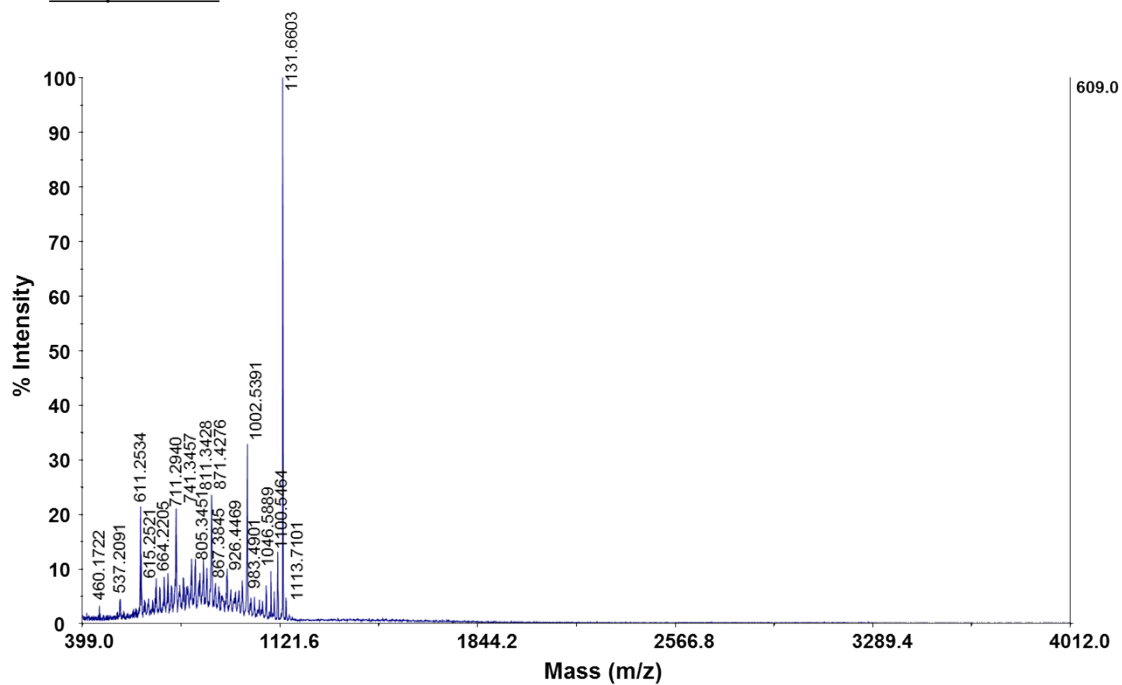
Compound 15



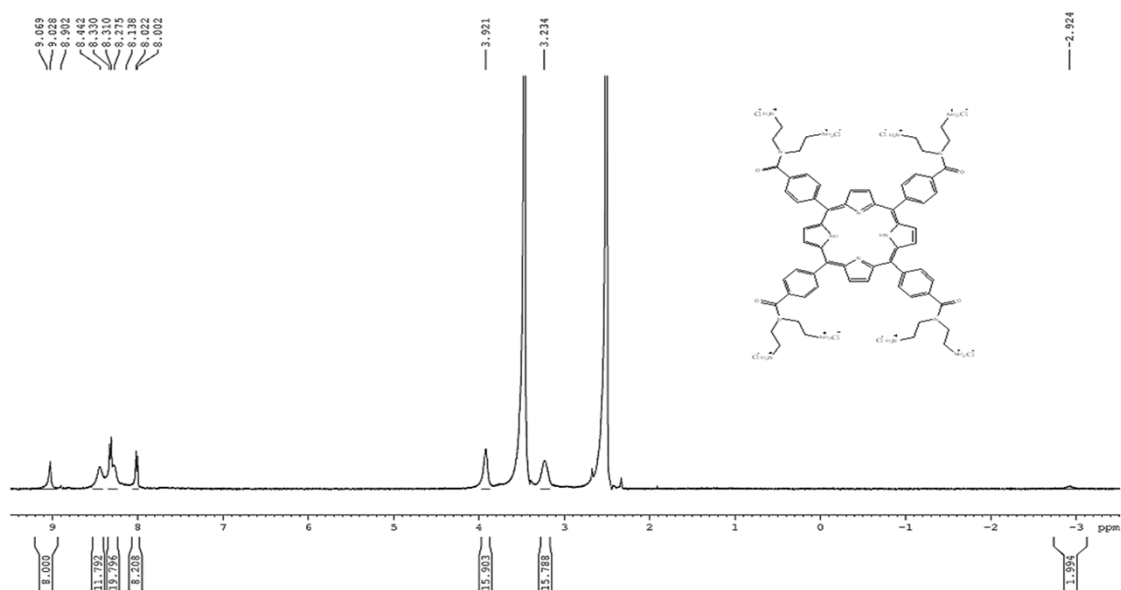
Compound 15



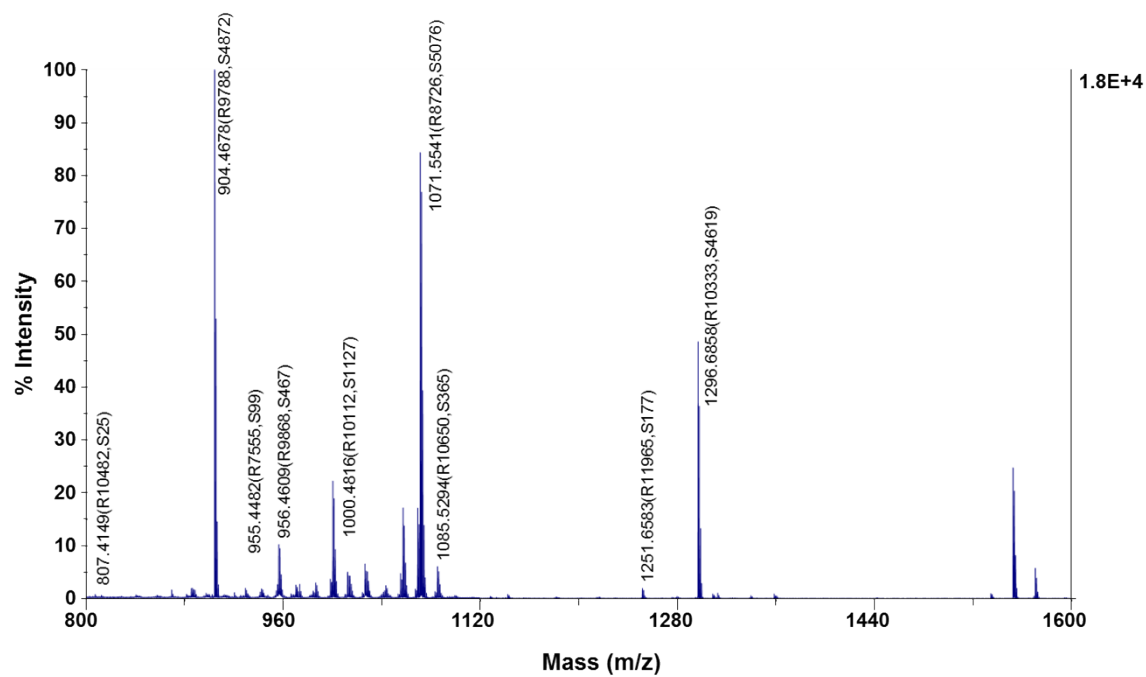
Compound 16



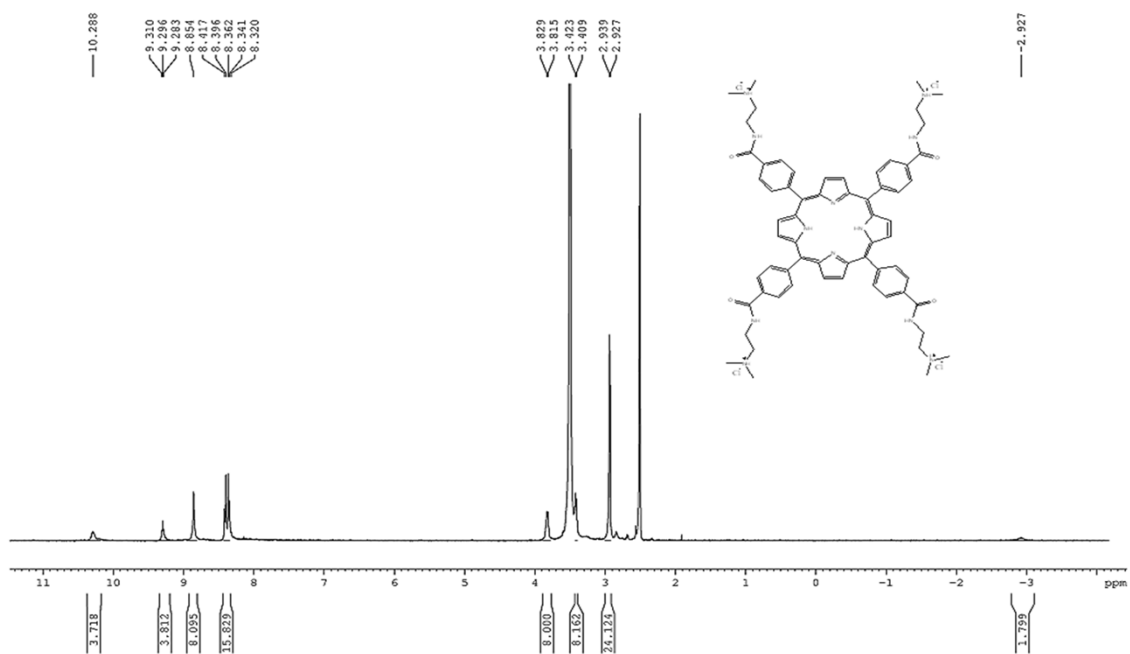
Compound 16



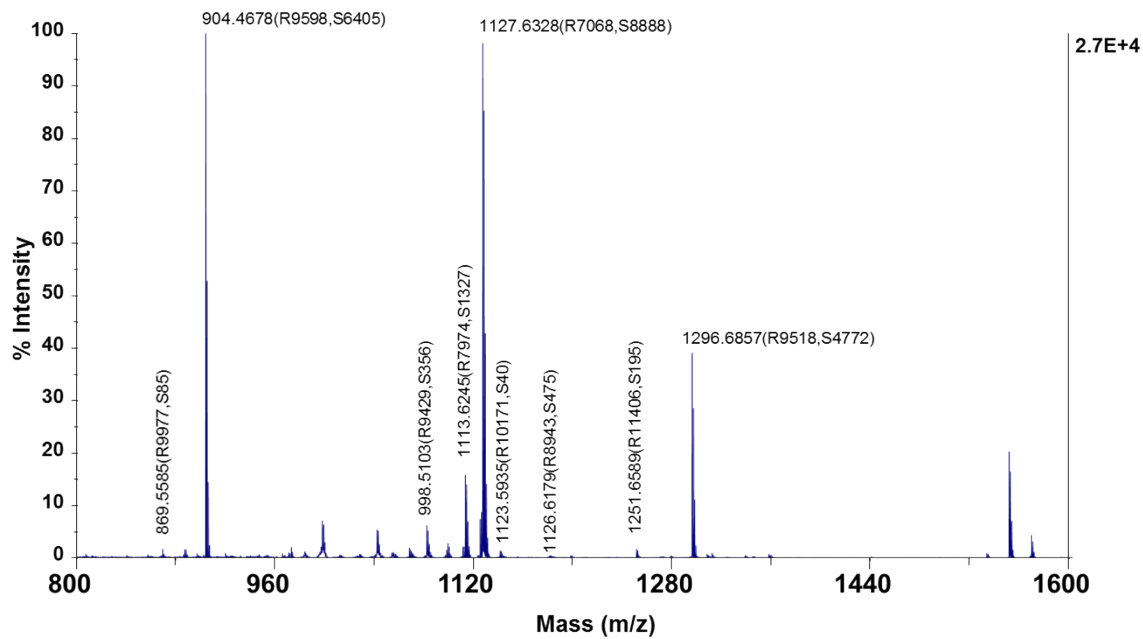
Compound 17



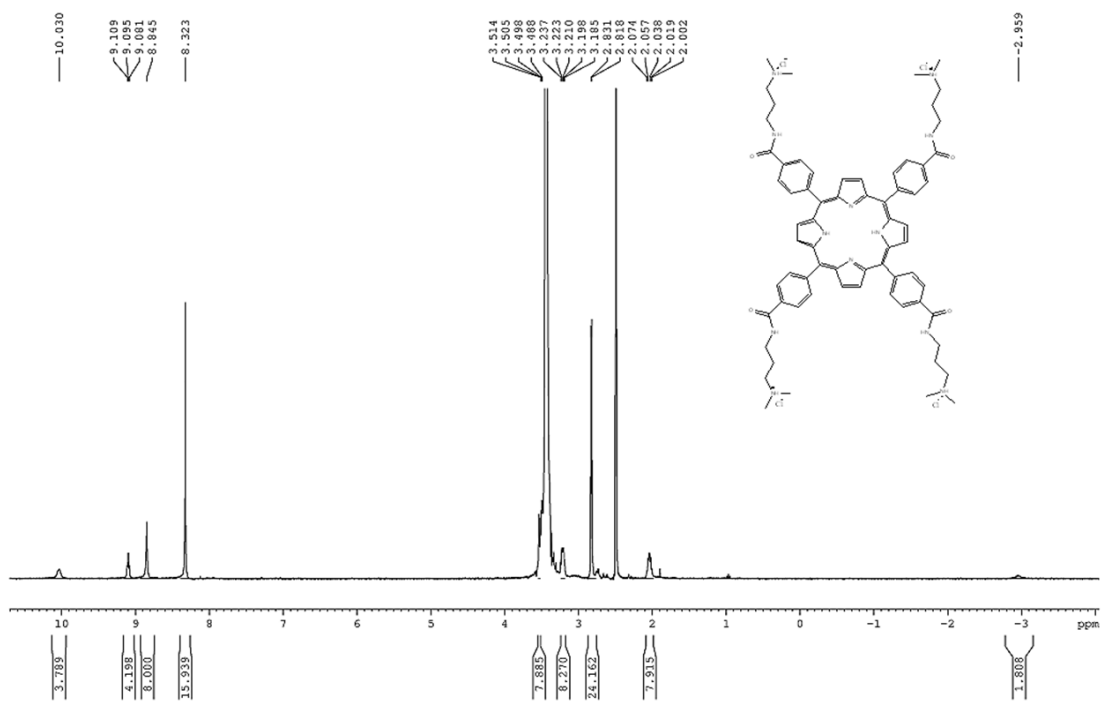
Compound 17



Compound 18



Compound 18



REFERENCES

- 1 M. V. Sokolov, O. Shamotienko, S. N. Dhochartaigh, J. T. Sack, and J. O. Dolly, *Neuropharmacology*, 2007, **53**, 272.
- 2 A. Al-Sabi, S. K. Kaza, J. O. Dolly, and J. Wang, *Biochem J*, 2013, **454**, 101.
- 3 S. B. Long, E. B. Campbell, and R. Mackinnon, *Science*, 2005, **309**, 897.
- 4 C. Ader, R. Schneider, S. Hornig, P. Velisetty, E. M. Wilson, A. Lange, K. Giller, I. Ohmert, M. F. Martin-Eaucclair, D. Trauner, S. Becker, O. Pongs, and M. Baldus, *Nat Struct Mol Biol*, 2008, **15**, 605.
- 5 J. H. Lee, B. H. Lee, S. H. Choi, I. S. Yoon, M. K. Pyo, T. J. Shin, W. S. Choi, Y. Lim, H. Rhim, K. H. Won, Y. W. Lim, H. Choe, D. H. Kim, Y. I. Kim, and S. Y. Nah, *Mol Pharmacol*, 2008, **73**, 619.
- 6 V. Martos, S. C. Bell, E. Santos, E. Y. Isacoff, D. Trauner, and J. de Mendoza, *Proc Natl Acad Sci U S A*, 2009, **106**, 10482.
- 7 S. Marzian, P. J. Stansfeld, M. Rapedius, S. Rinne, E. Nematian-Ardestani, J. L. Abbruzzese, K. Steinmeyer, M. S. Sansom, M. C. Sanguinetti, T. Baukrowitz, and N. Decher, *Nat Chem Biol*, 2013, **9**, 507.
- 8 S. Pegoraro, M. Lang, T. Dreker, J. Kraus, S. Hamm, C. Meere, J. Feurle, S. Tasler, S. Prutting, Z. Kuras, V. Visan, and S. Grissmer, *Bioorg Med Chem Lett*, 2009, **19**, 2299.
- 9 S. Rangaraju, K. K. Khoo, Z. P. Feng, G. Crossley, D. Nugent, I. Khaytin, V. Chi, C. Pham, P. Calabresi, M. W. Pennington, R. S. Norton, and K. G. Chandy, *J Biol Chem*, 2010, **285**, 9124.
- 10 Q. Yang, L. Du, X. Wang, M. Li, and Q. You, *J Mol Graph Model*, 2008, **27**, 178.
- 11 A. Sali and T. L. Blundell, *J Mol Biol*, 1993, **234**, 779.
- 12 A. Sali and J. P. Overington, *Protein Sci*, 1994, **3**, 1582.
- 13 J. U. Bowie, R. Luthy, and D. Eisenberg, *Science*, 1991, **253**, 164.
- 14 R. A. Laskowski, J. A. Rullmann, M. W. MacArthur, R. Kaptein, and J. M. Thornton, *J Biomol NMR*, 1996, **8**, 477.
- 15 C. Colovos and T. O. Yeates, *Protein Sci*, 1993, **2**, 1511.
- 16 D. S. DeLano WL., 'The PyMOL Molecular Graphics System', Palo Alto, 2002.
- 17 G. Wu, D. H. Robertson, C. L. Brooks, 3rd, and M. Vieth, *J Comput Chem*, 2003, **24**, 1549.
- 18 S. N. Gradl, J. P. Felix, E. Y. Isacoff, M. L. Garcia, and D. Trauner, *J Am Chem Soc*, 2003, **125**, 12668
- 19 H-J. Schneider and M. Wang, *J Org Chem*, 1994, **59**, 7473-7478.