Supporting Information

Transmembrane anion transport and cytotoxicity of synthetic tambjamine analogs.

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Characterization data

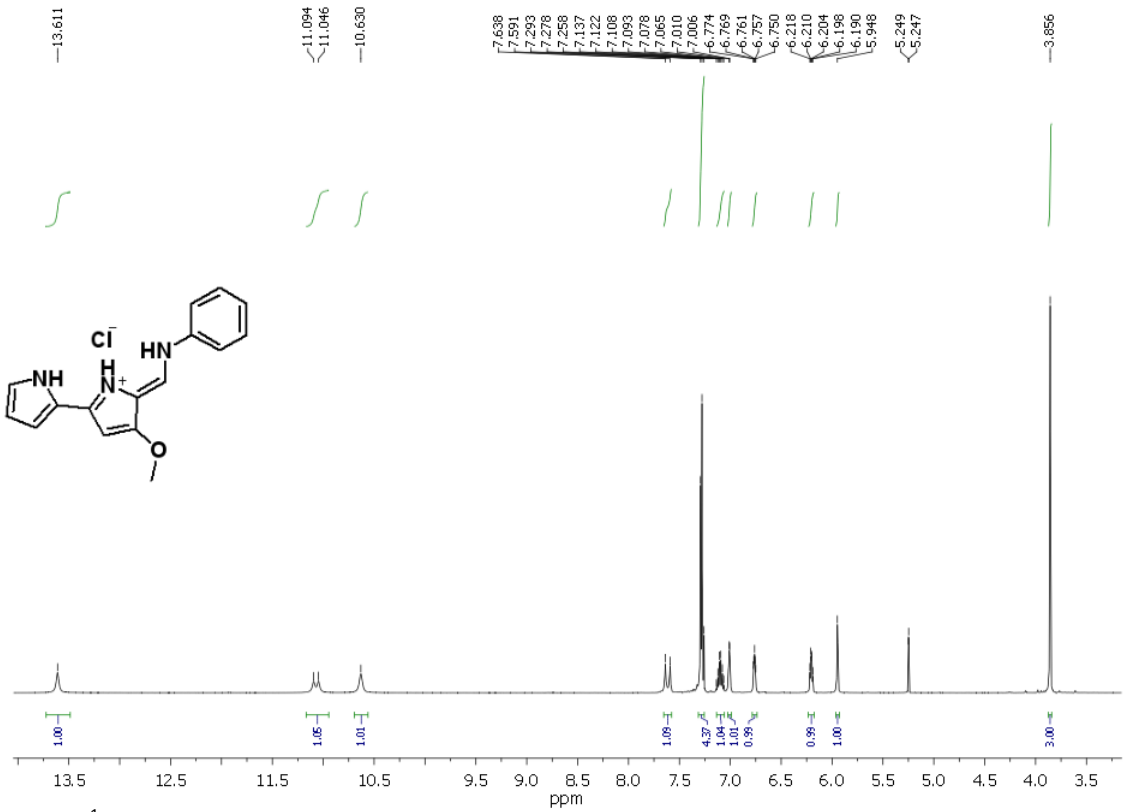

Figure S1. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **1**. HCl.

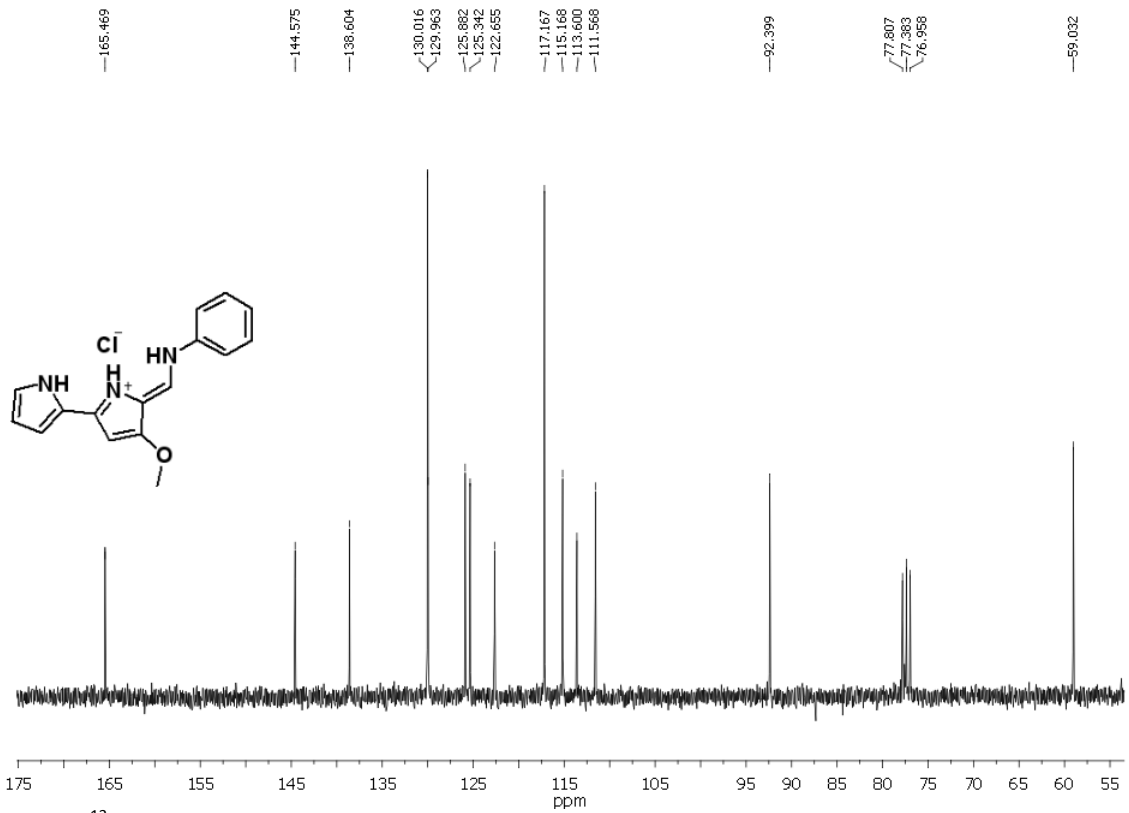

Figure S2. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **1**. HCl.

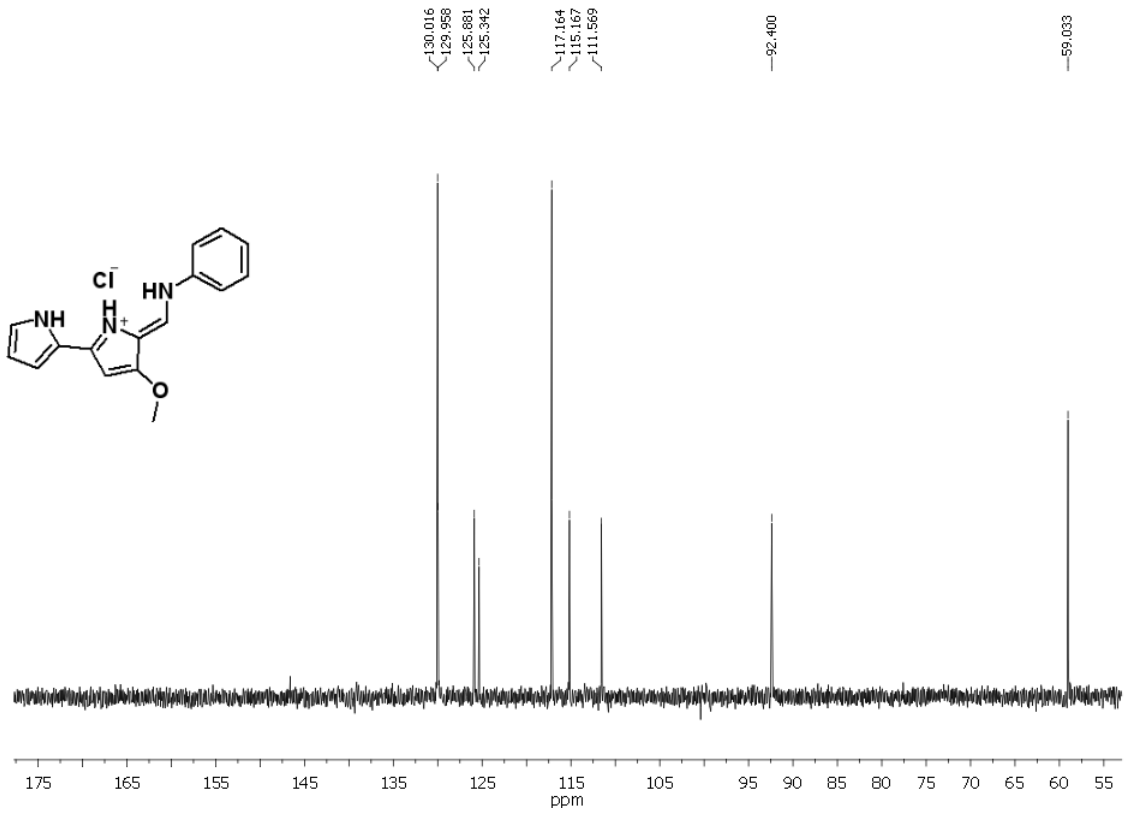

Figure S3. DEPT ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **1**. HCl.

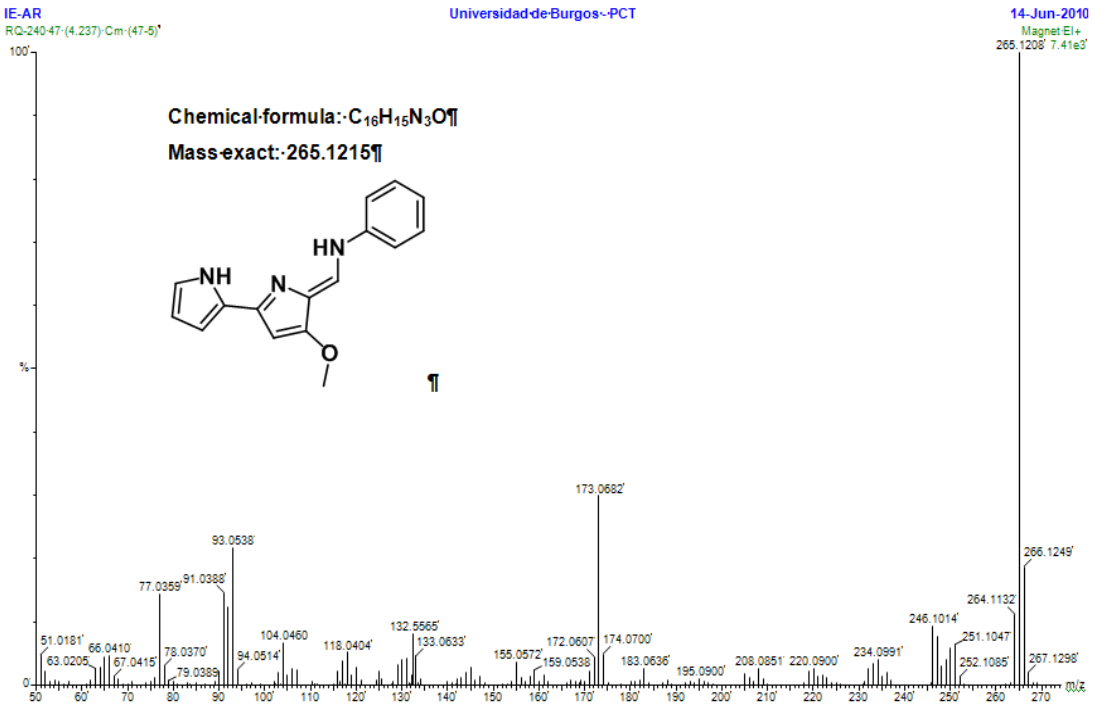

Figure S4. HRMS (EI) of compound **1**.

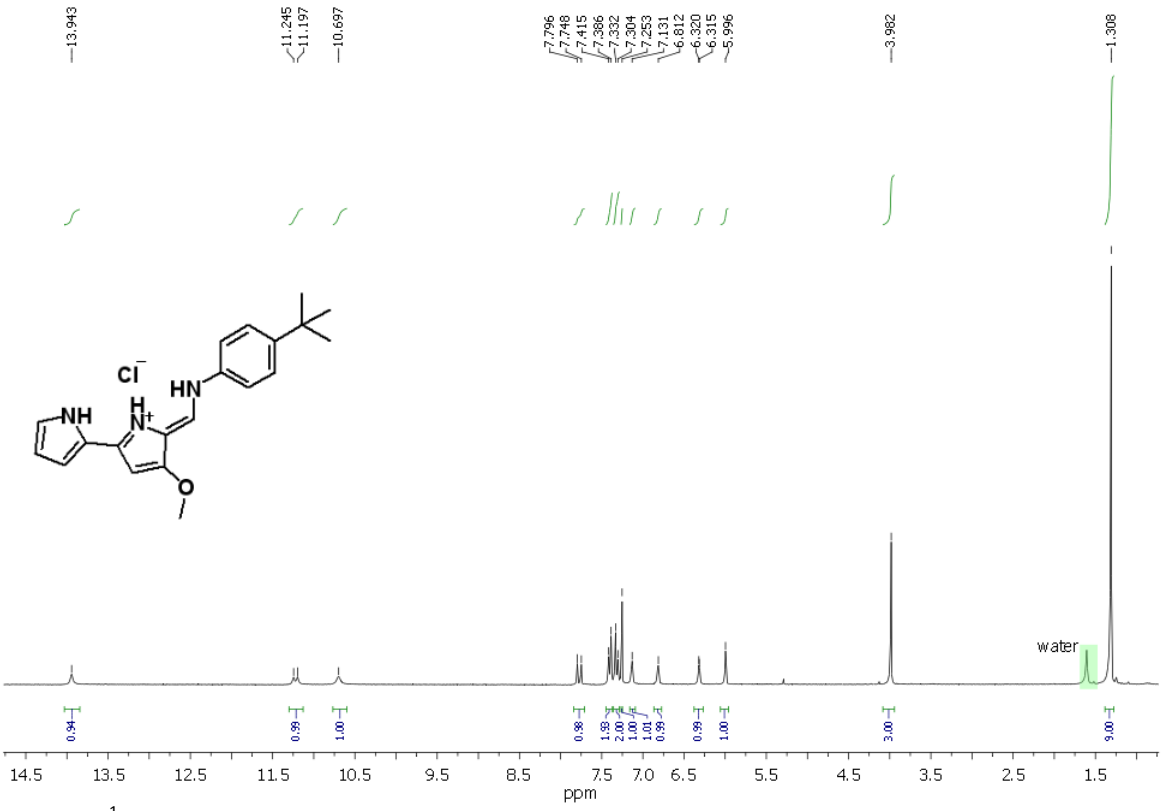

Figure S5. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **2**. HCl.

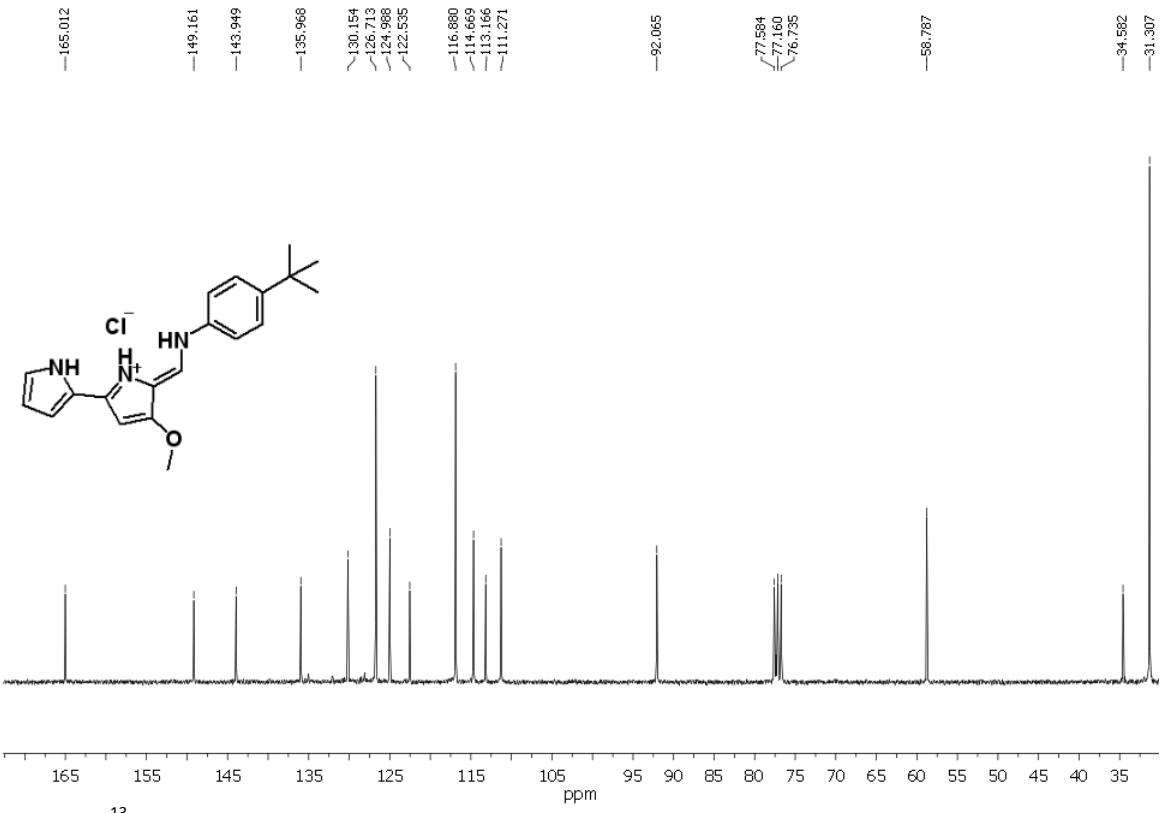

Figure S6. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **2**. HCl.

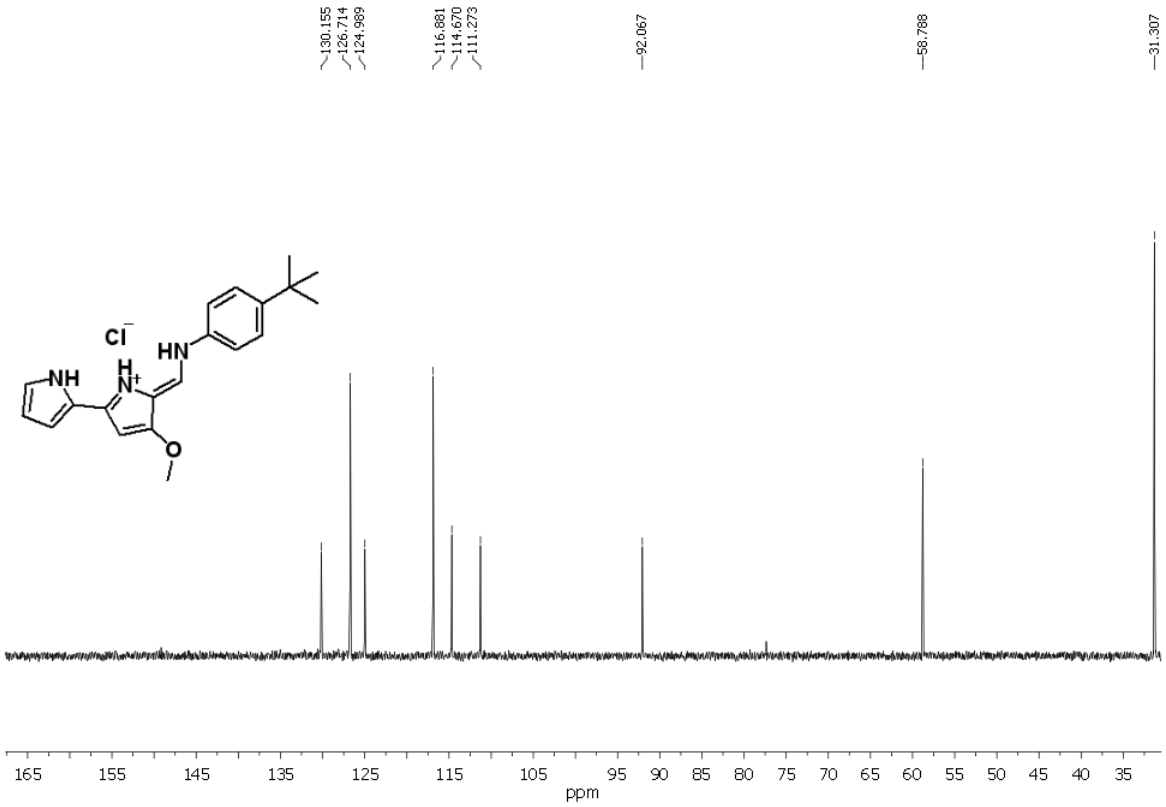

Figure S7. DEPT ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **2**. HCl.

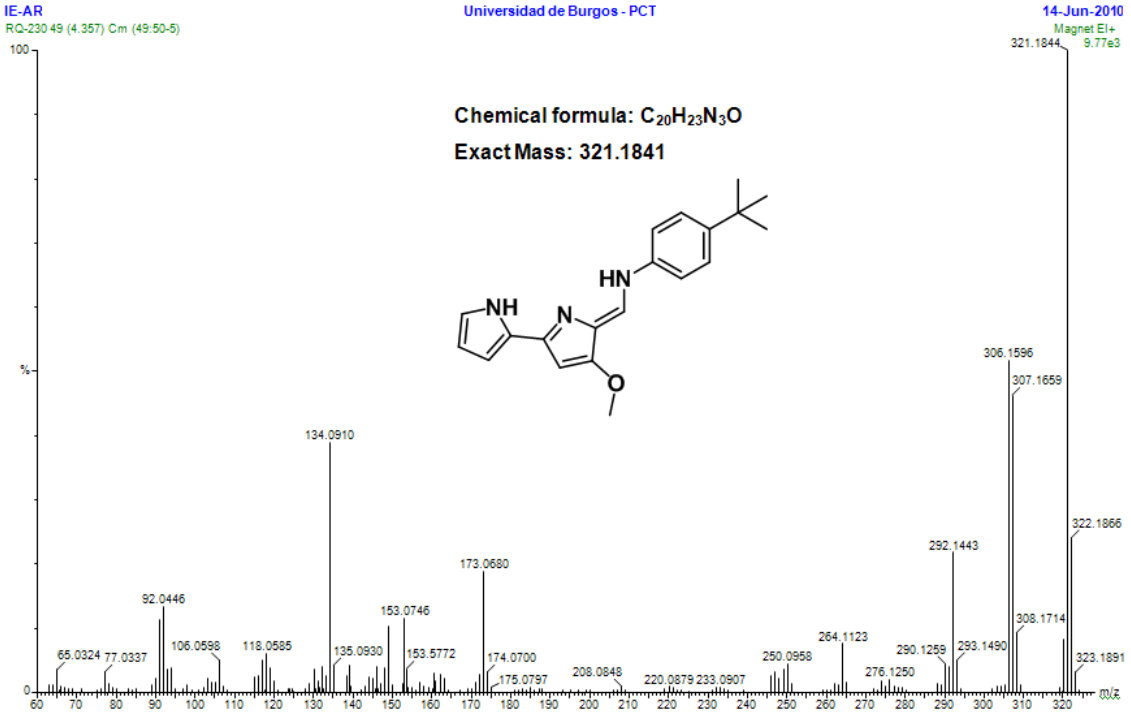

Figure S8. HRMS (EI) of compound **2**.

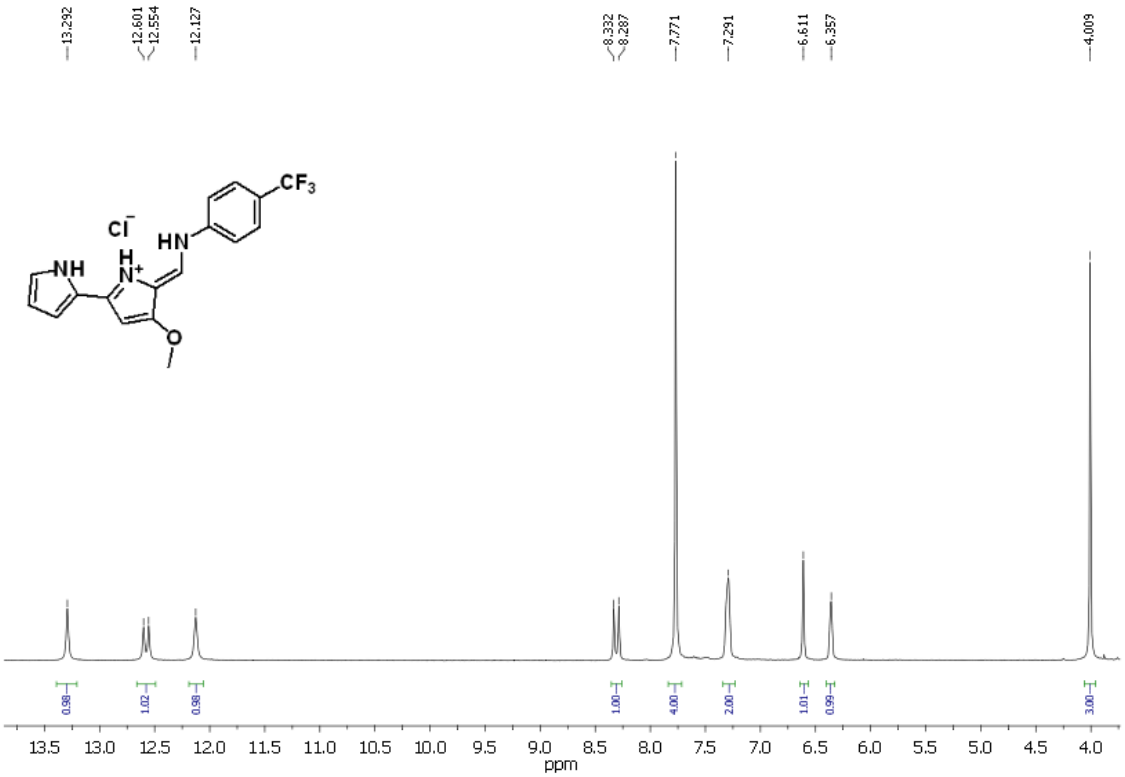

Figure S9. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **3**. HCl.

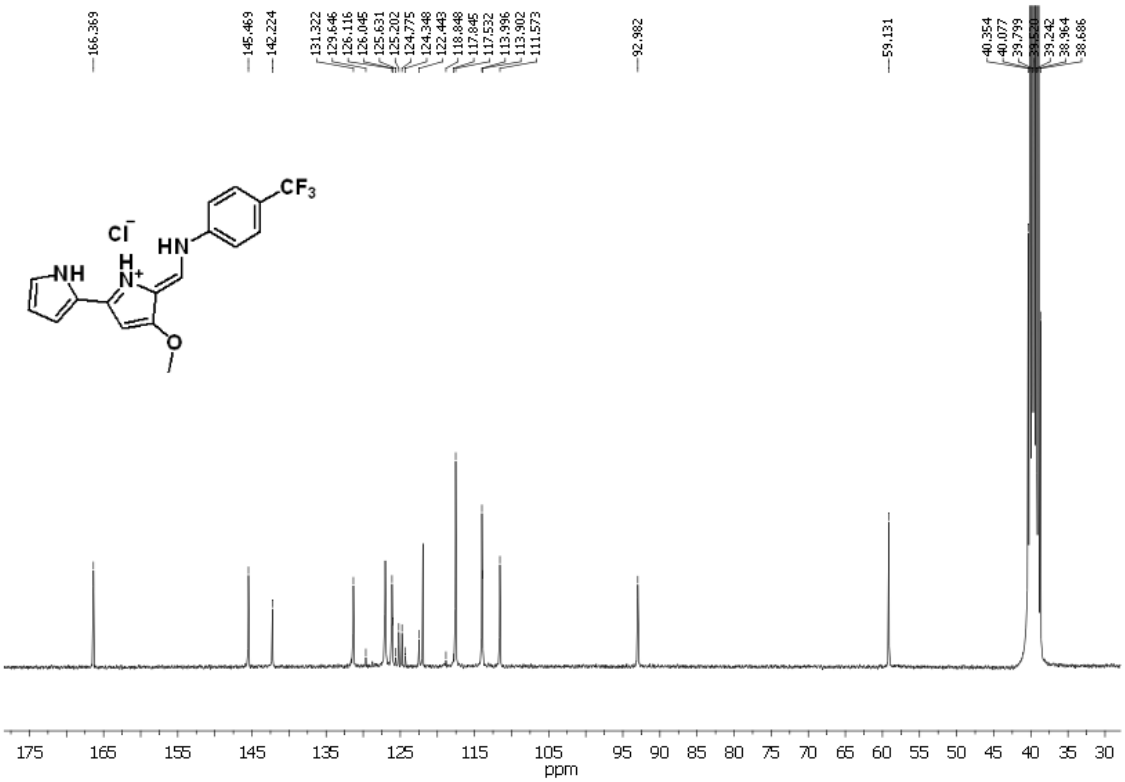

Figure S10. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **3**. HCl.

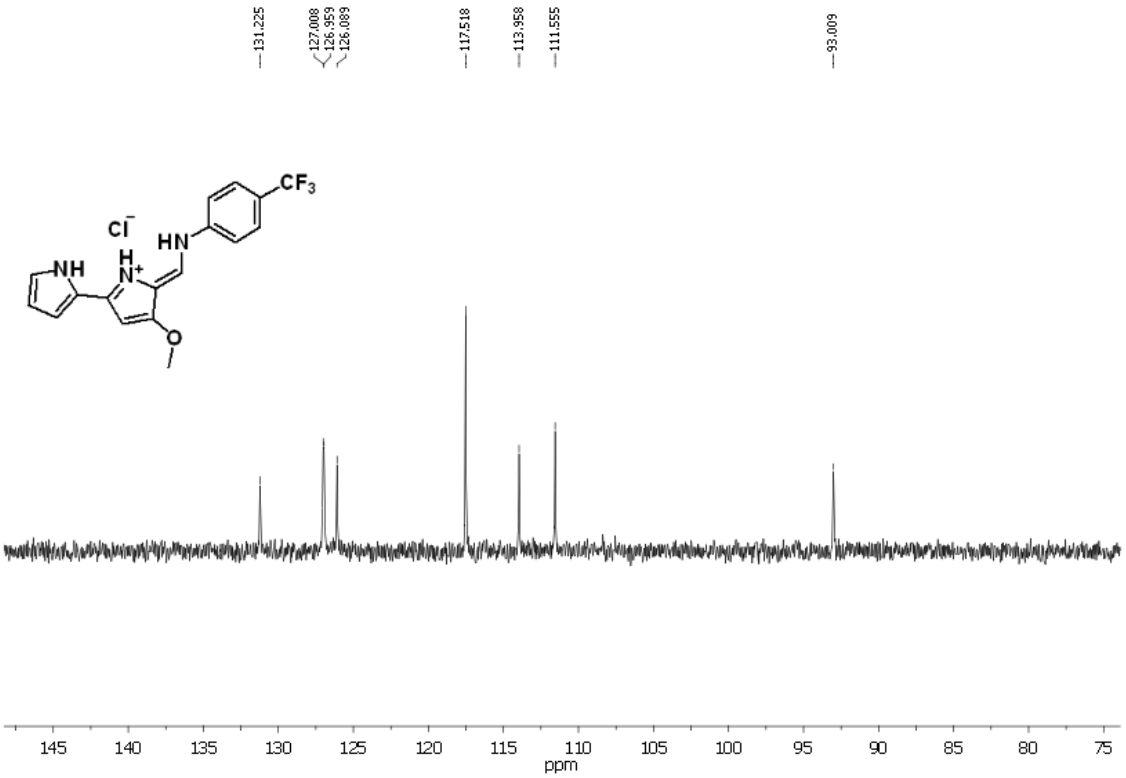

Figure S11. DEPT ^{13}C NMR (CDCl3, 75 MHz) of compound **3**. HCl.

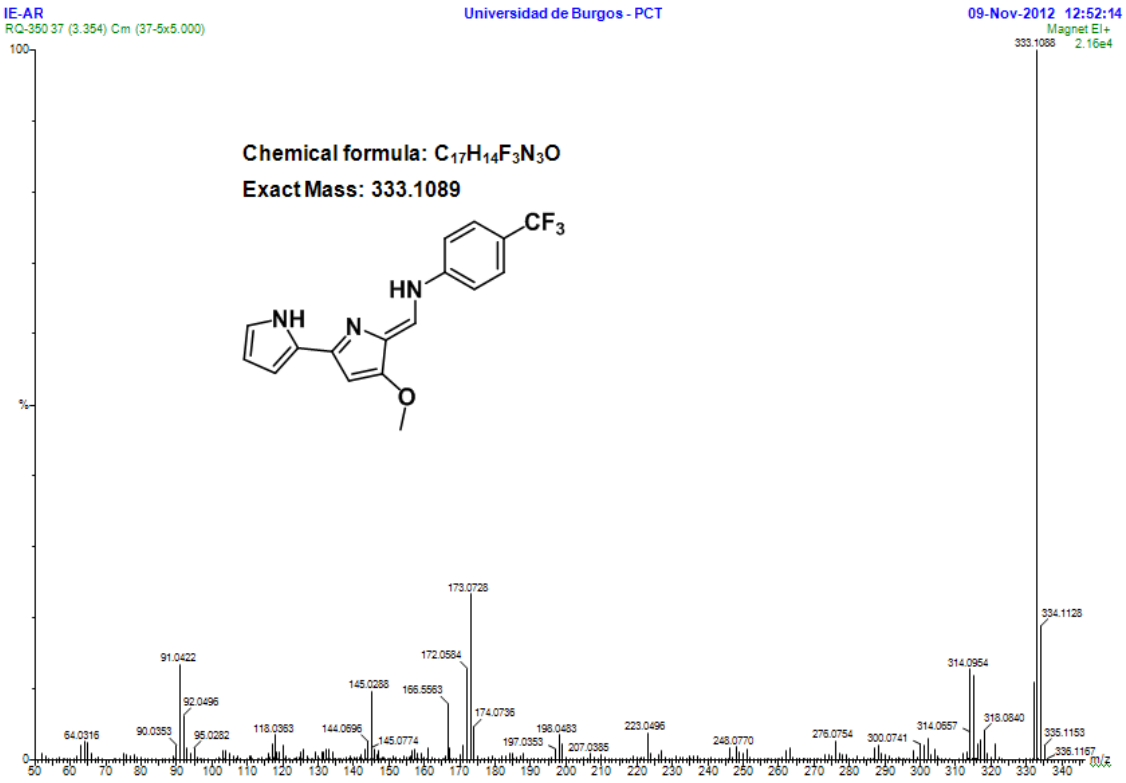

Figure S12. HRMS (EI) of compound **3**.

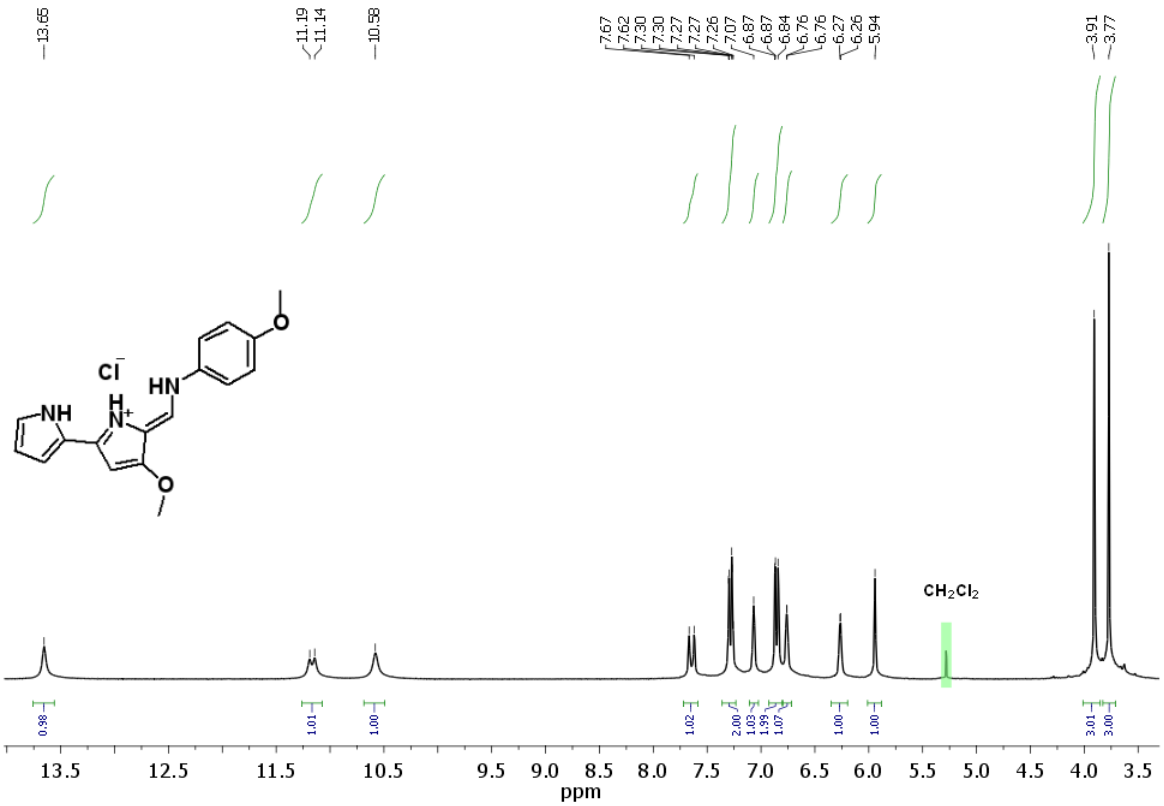

Figure S13. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **4**. HCl.

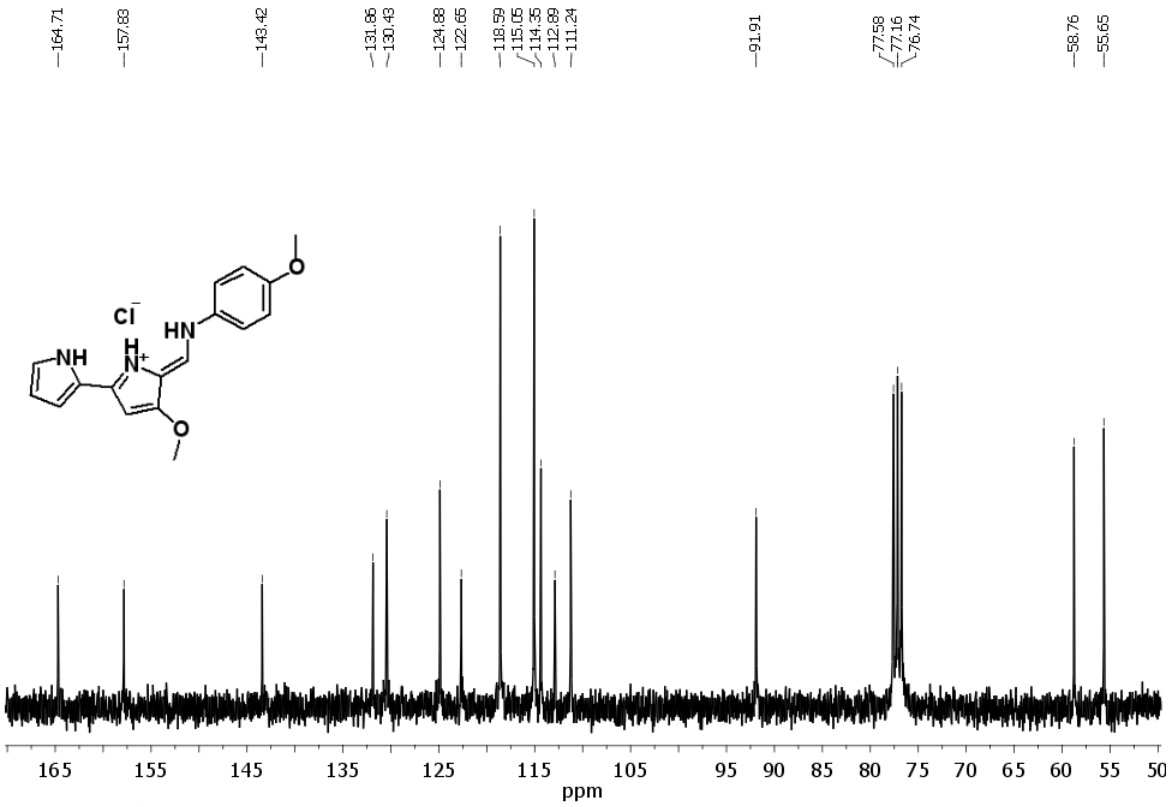

Figure S14. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **4**. HCl.

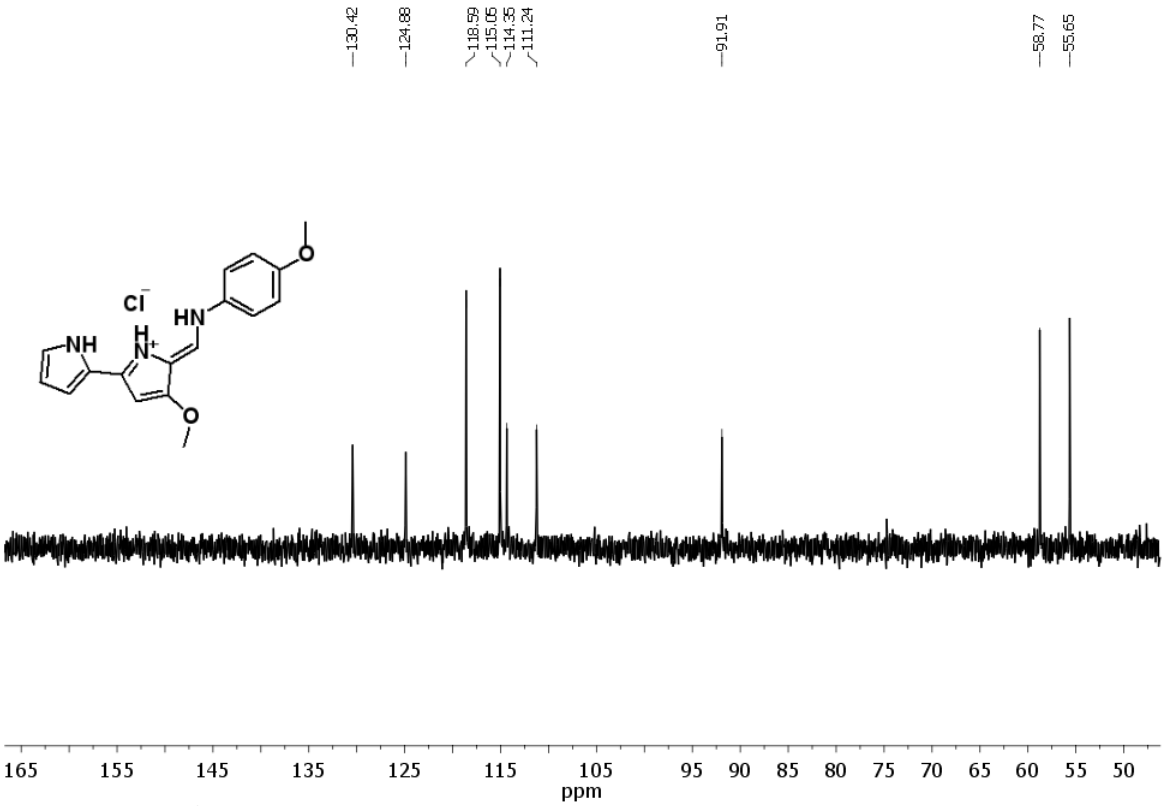

Figure S15. DEPT ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **4**. HCl.

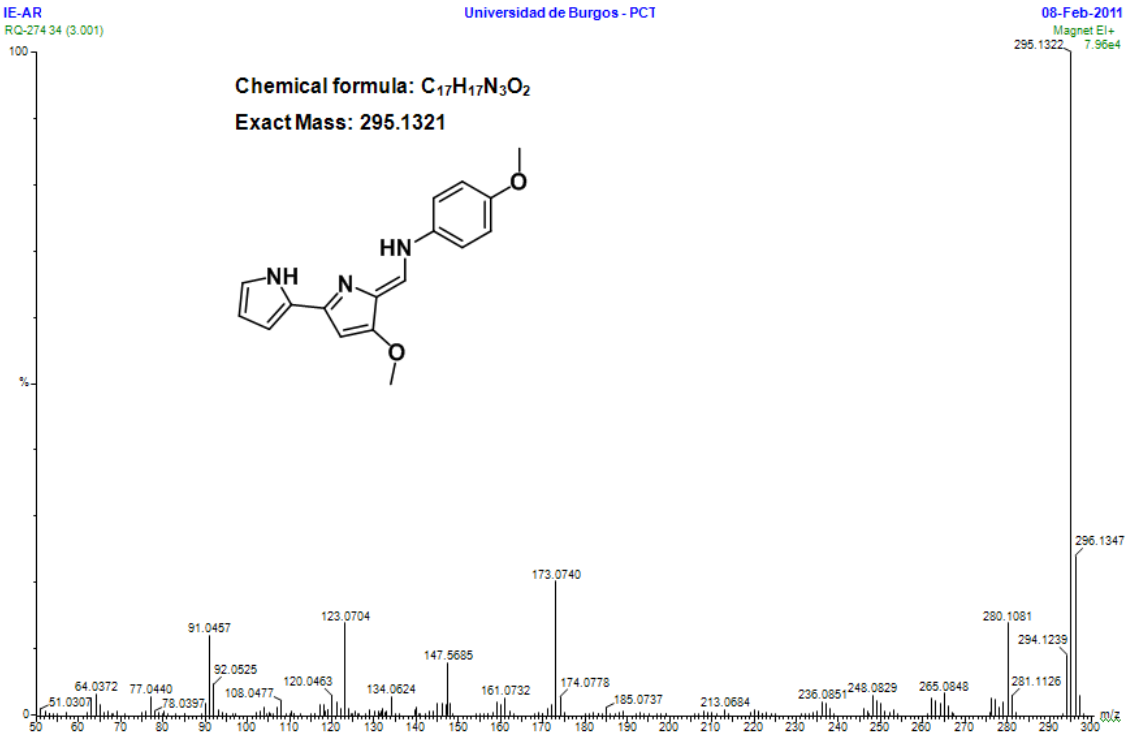

Figure S16. HRMS (EI) of compound **4**.

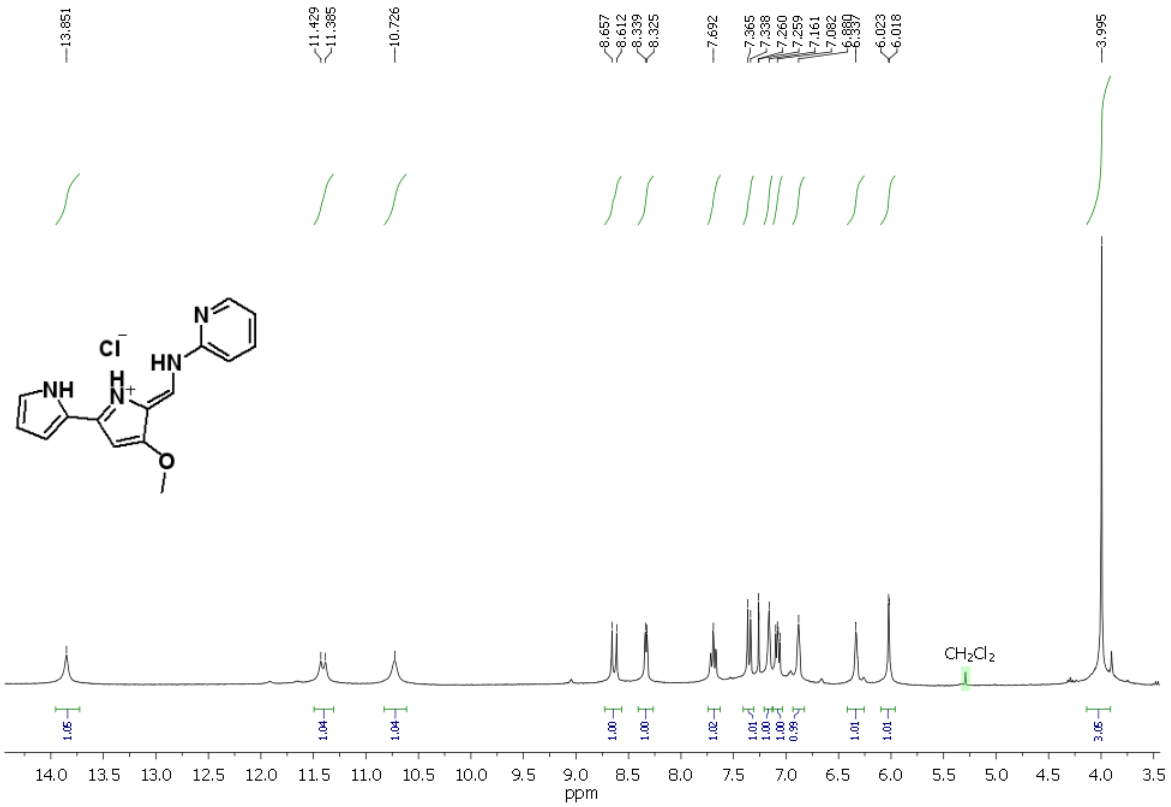

Figure S17. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **5**. HCl.

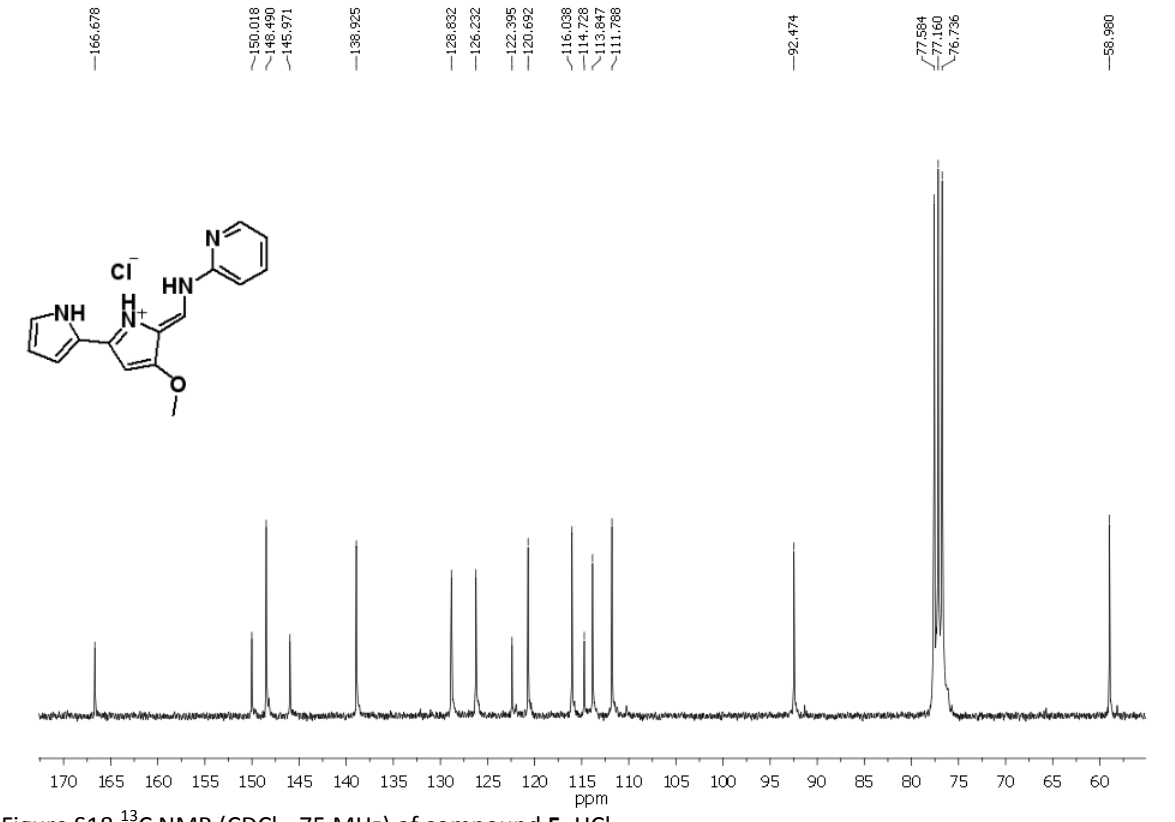

Figure S18.^{13}C NMR ($CDCl_3$, 75 MHz) of compound **5**. HCl.

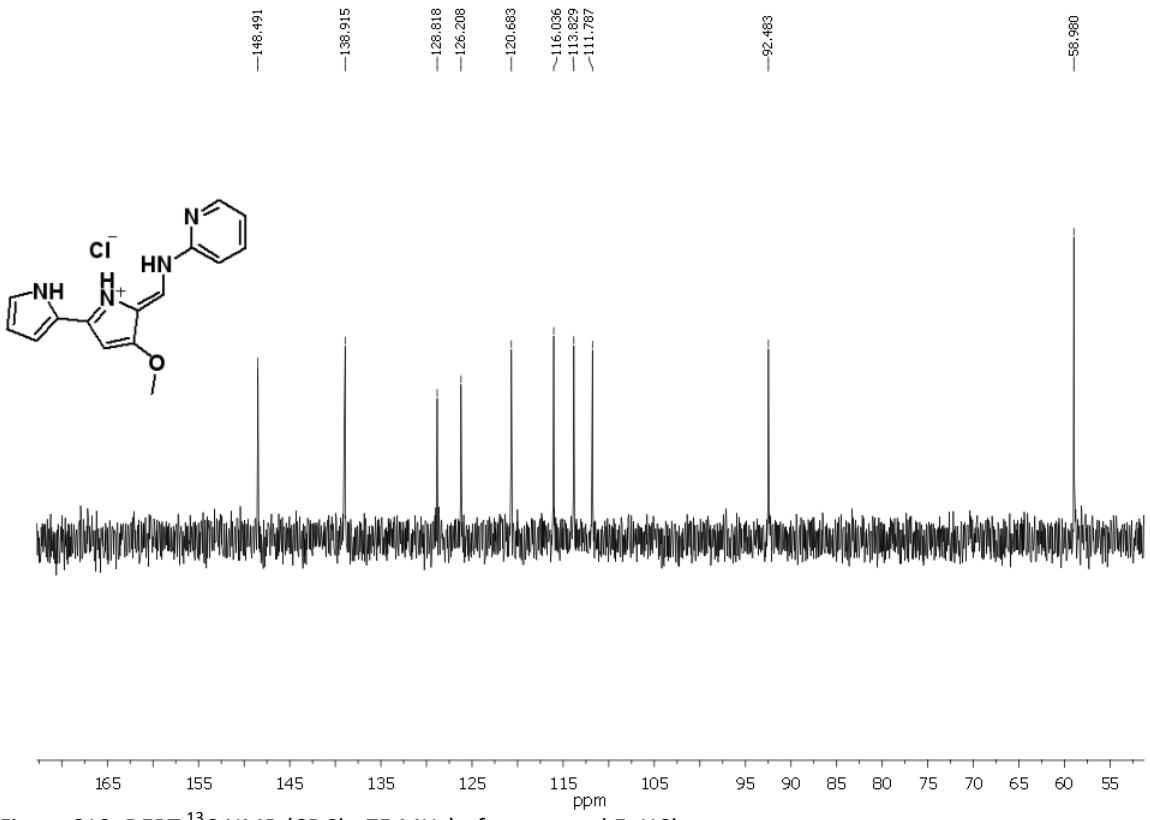

Figure S19. DEPT ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **5**. HCl.

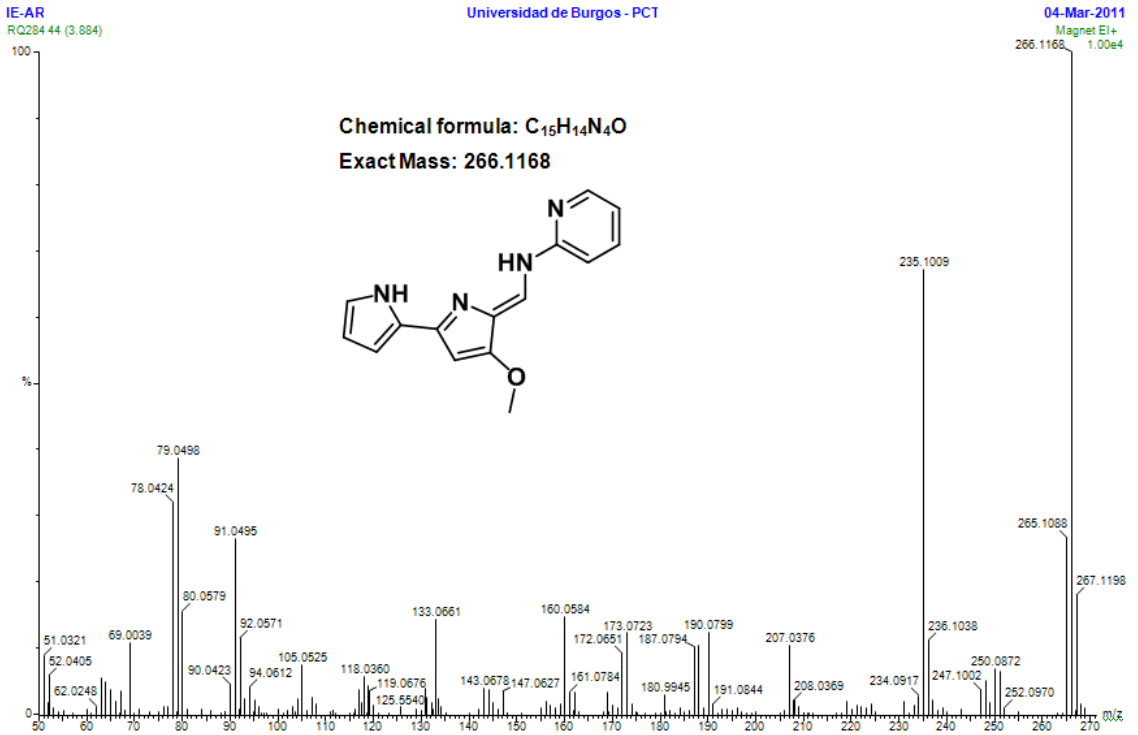

Figure S20. HRMS (EI) of compound **5**.

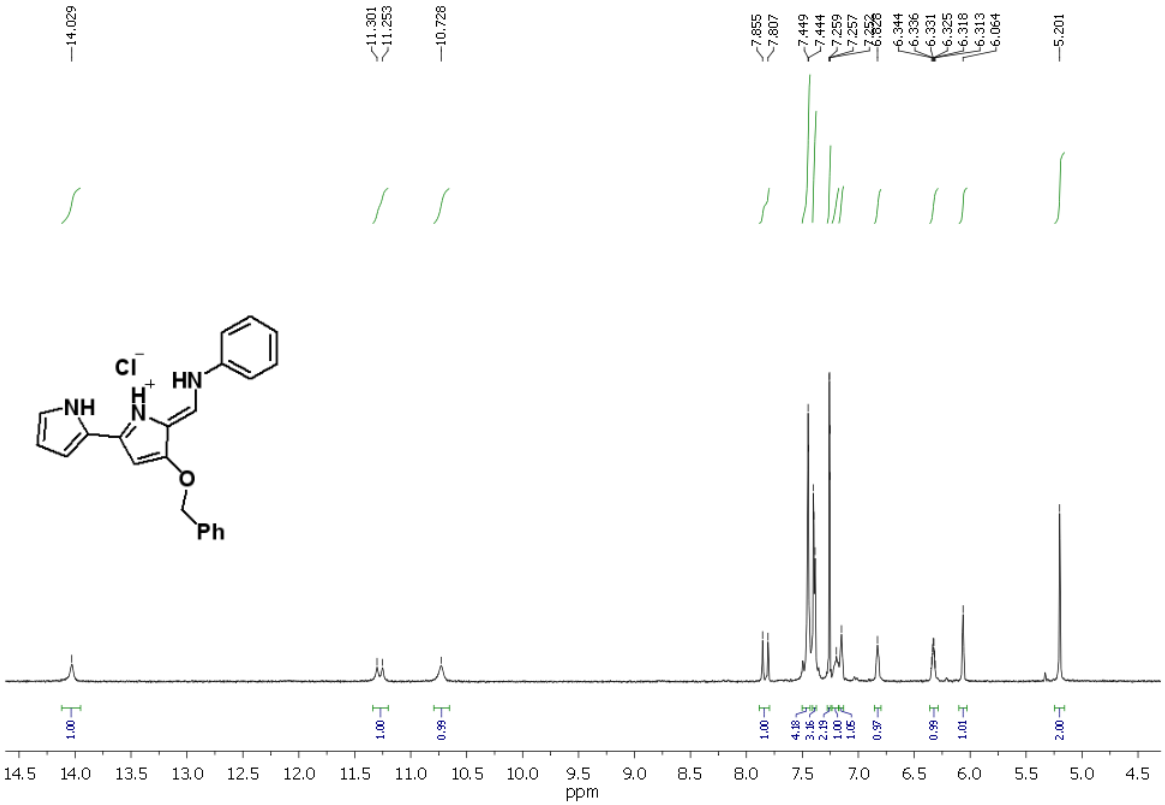

Figure S21. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **6**. HCl.

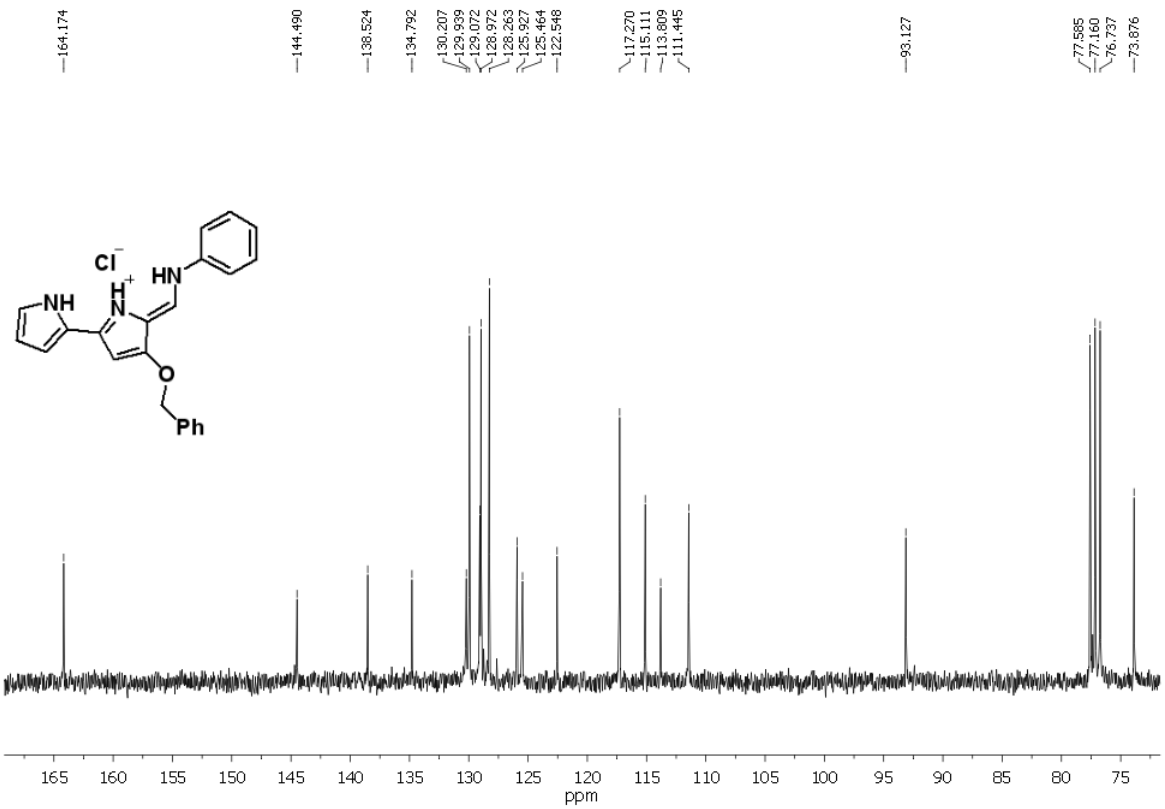

Figure S22. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **6**. HCl.

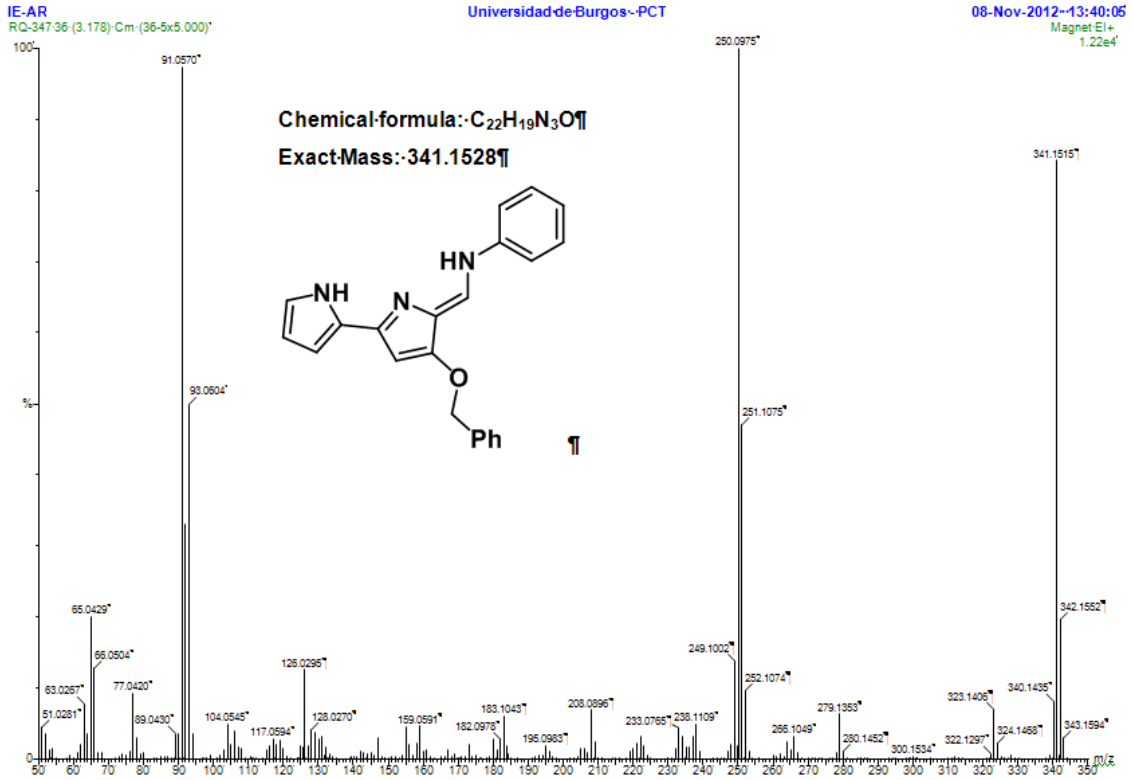

Figure S23. HRMS (EI) of compound **6**.

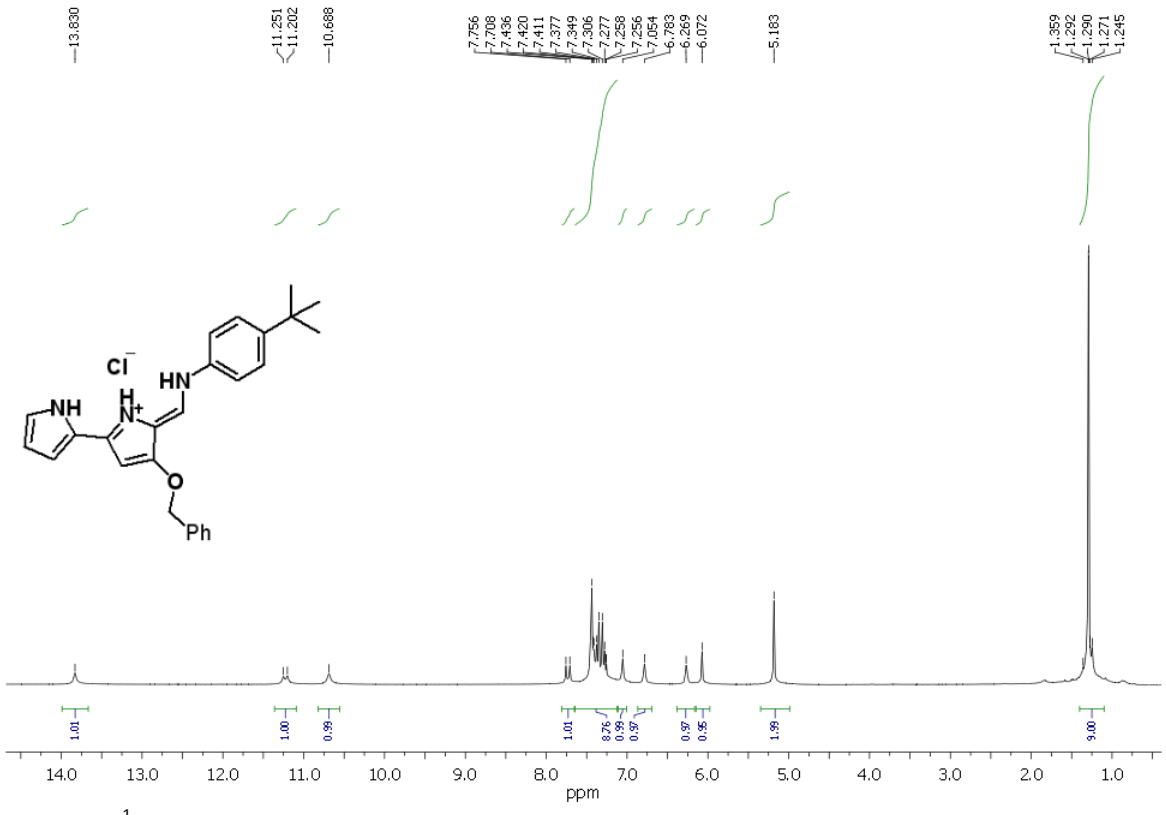

Figure S24. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **7**. HCl.

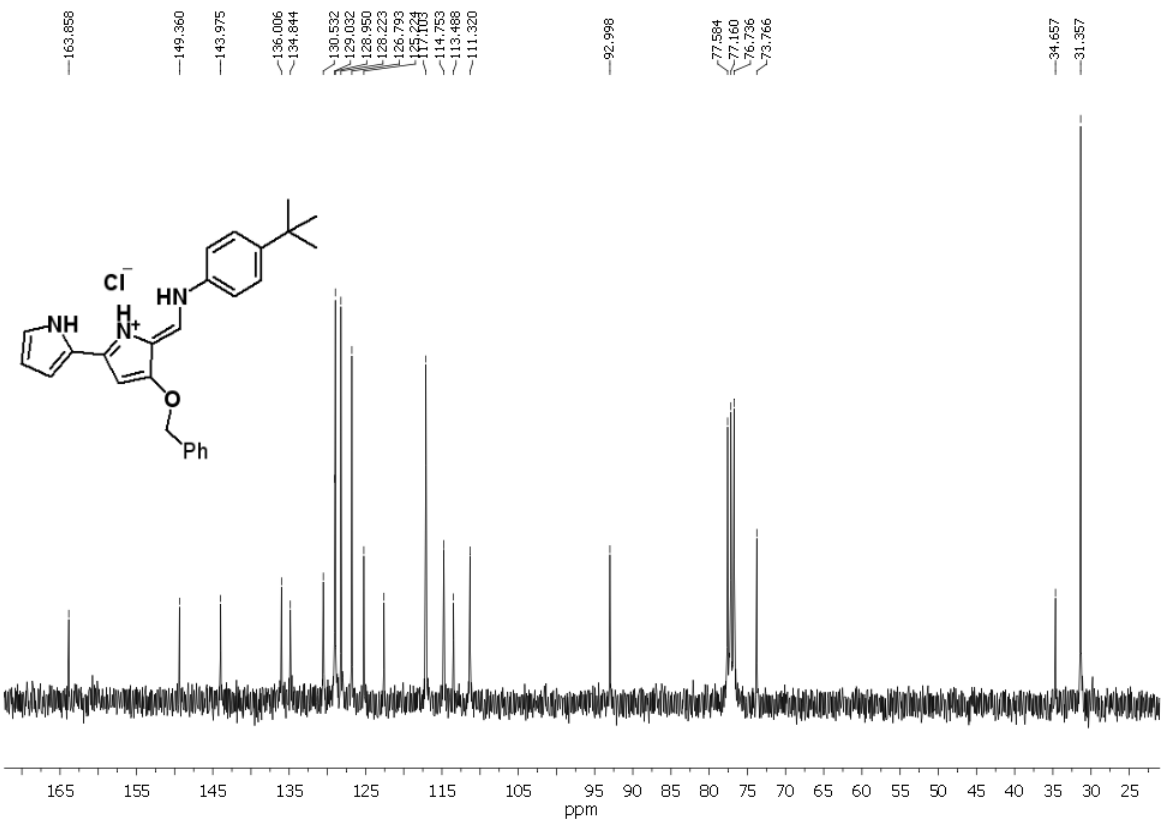

Figure S25. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **7**. HCl.

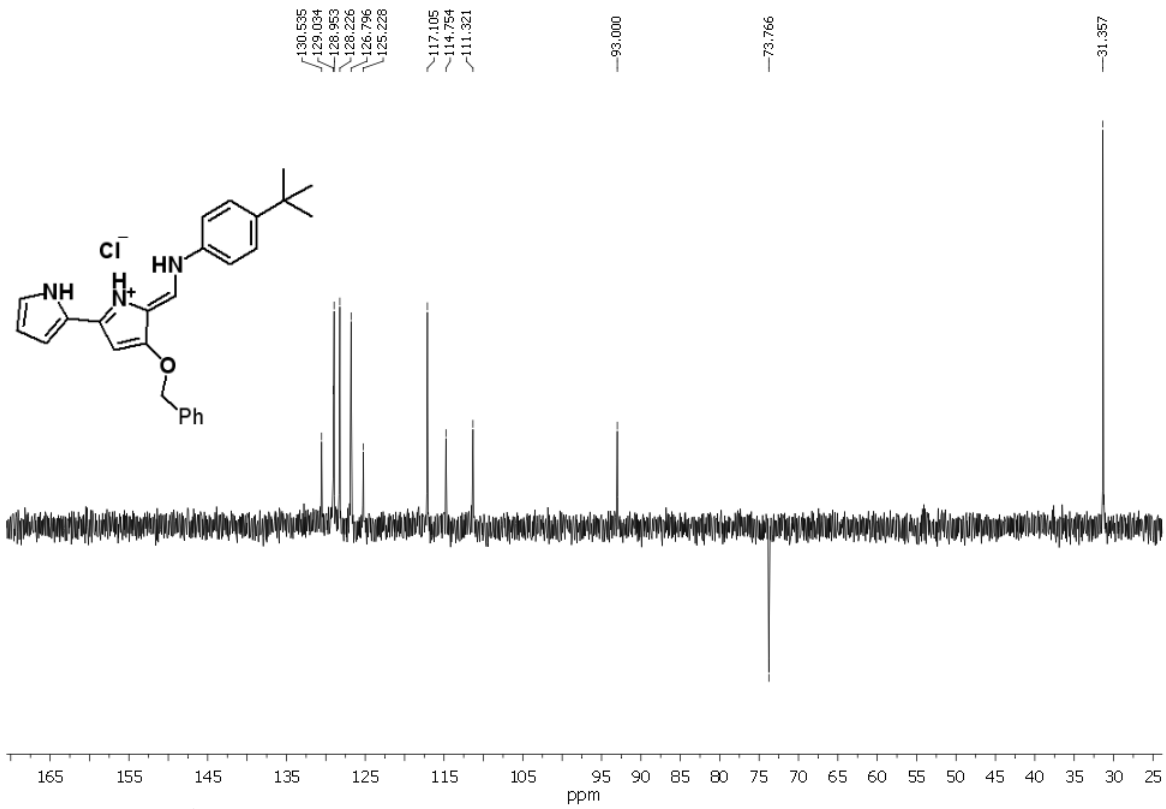

Figure S26. DEPT^{13}C NMR ($CDCl_3$, 75 MHz) of compound **7**. HCl.

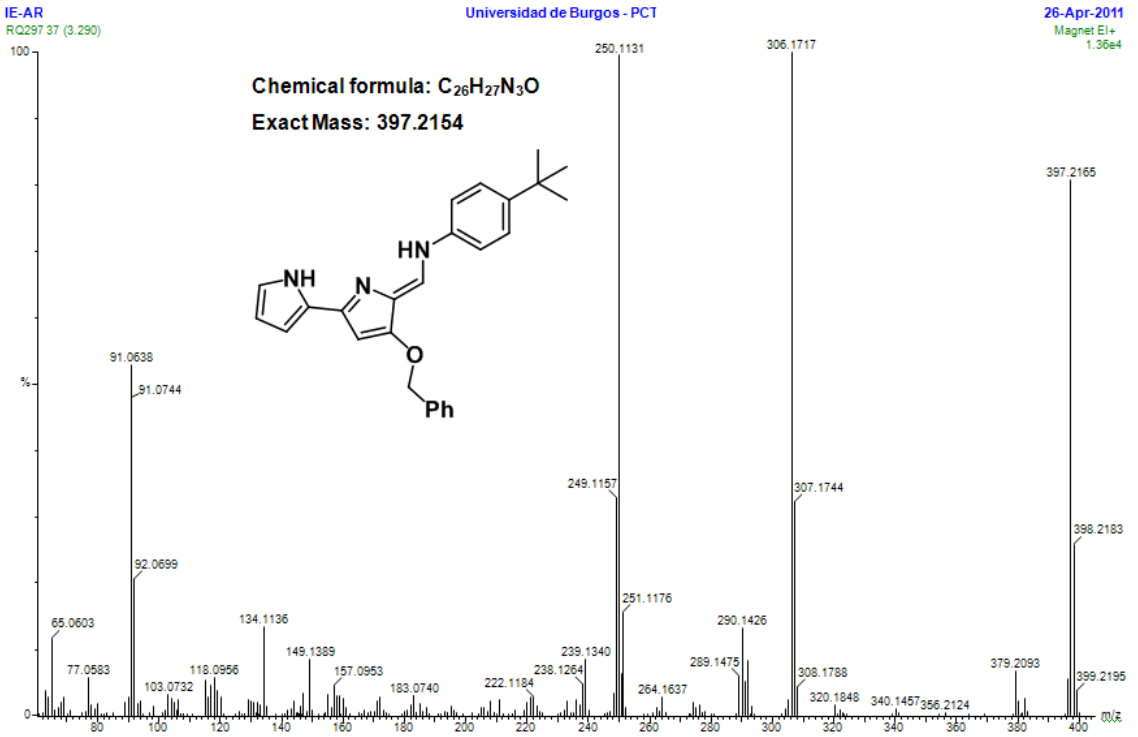

Figure S27. HRMS (EI) of compound **7**.

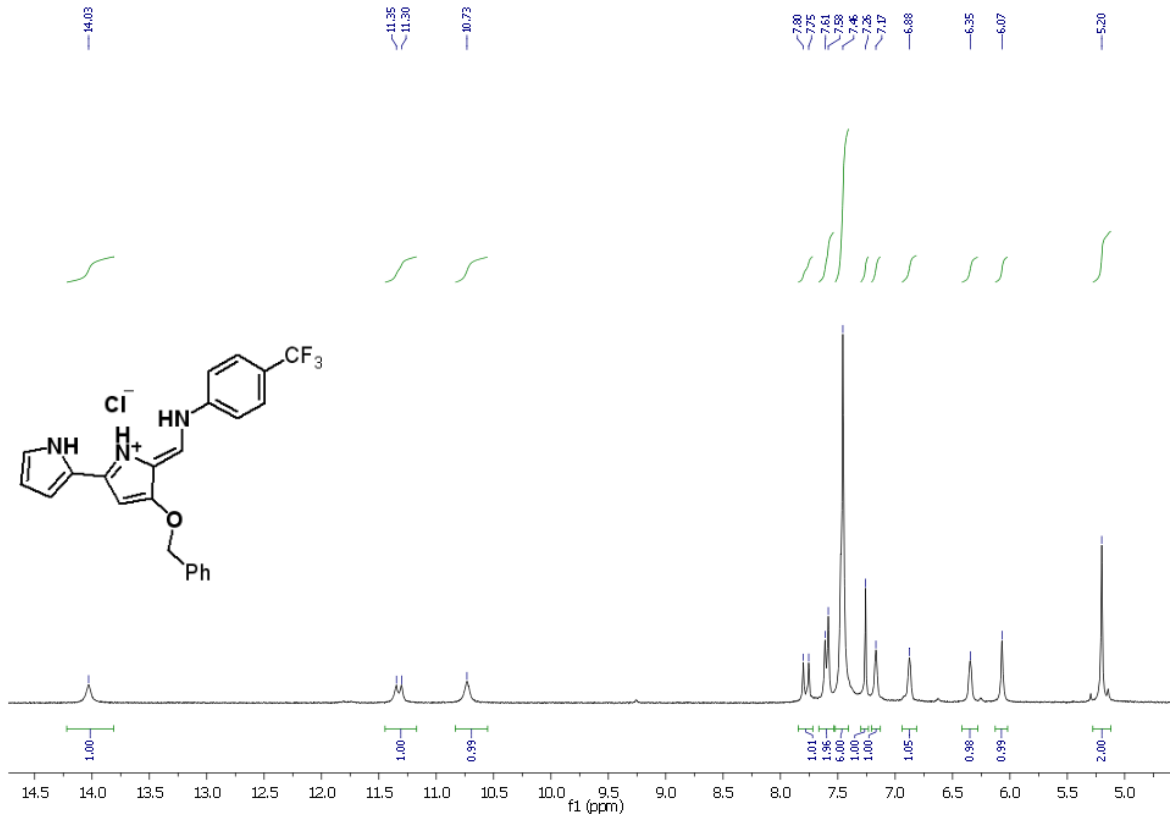

Figure S28. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **8**. HCl.

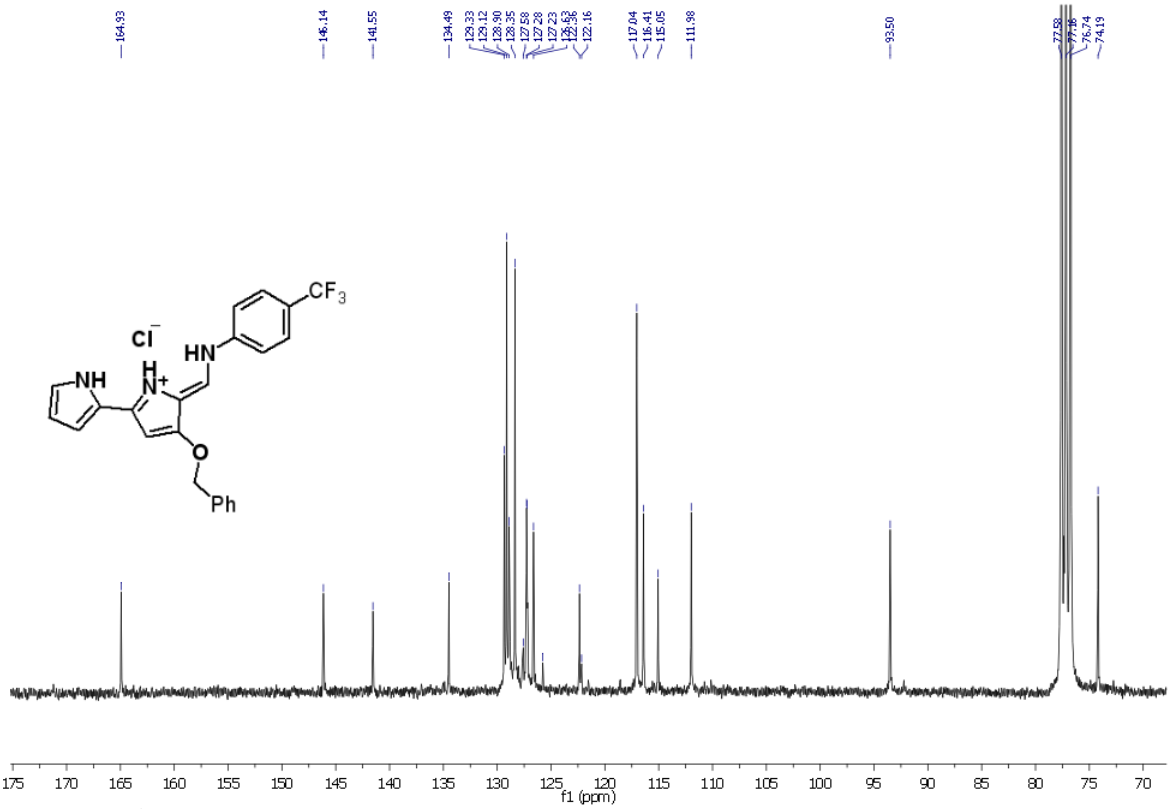

Figure S29. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **8**. HCl.

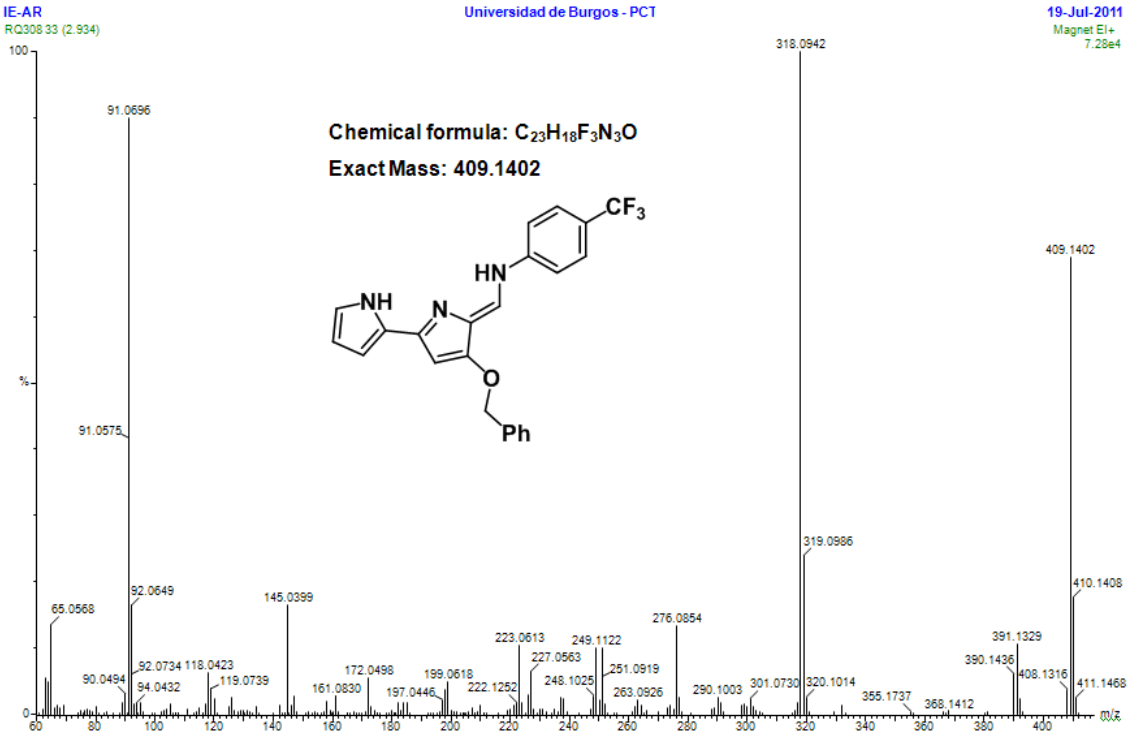

Figure S30. HRMS (EI) of compound **8**.

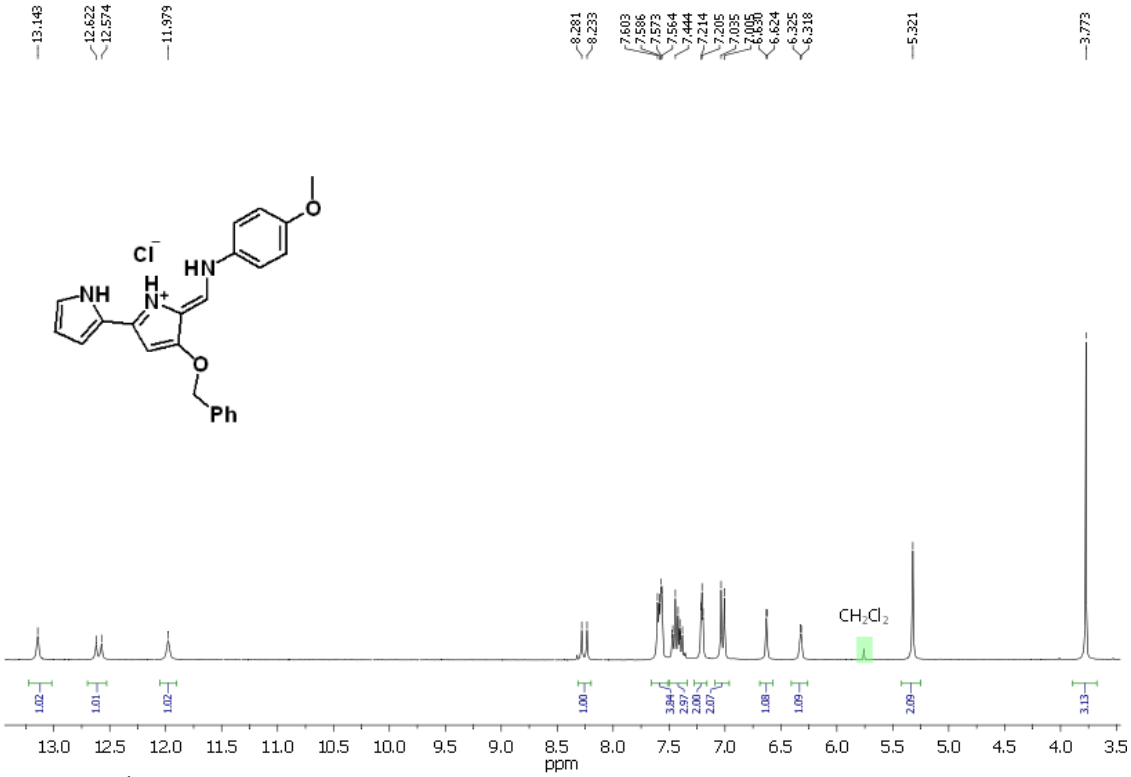

Figure S31. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **9**. HCl.

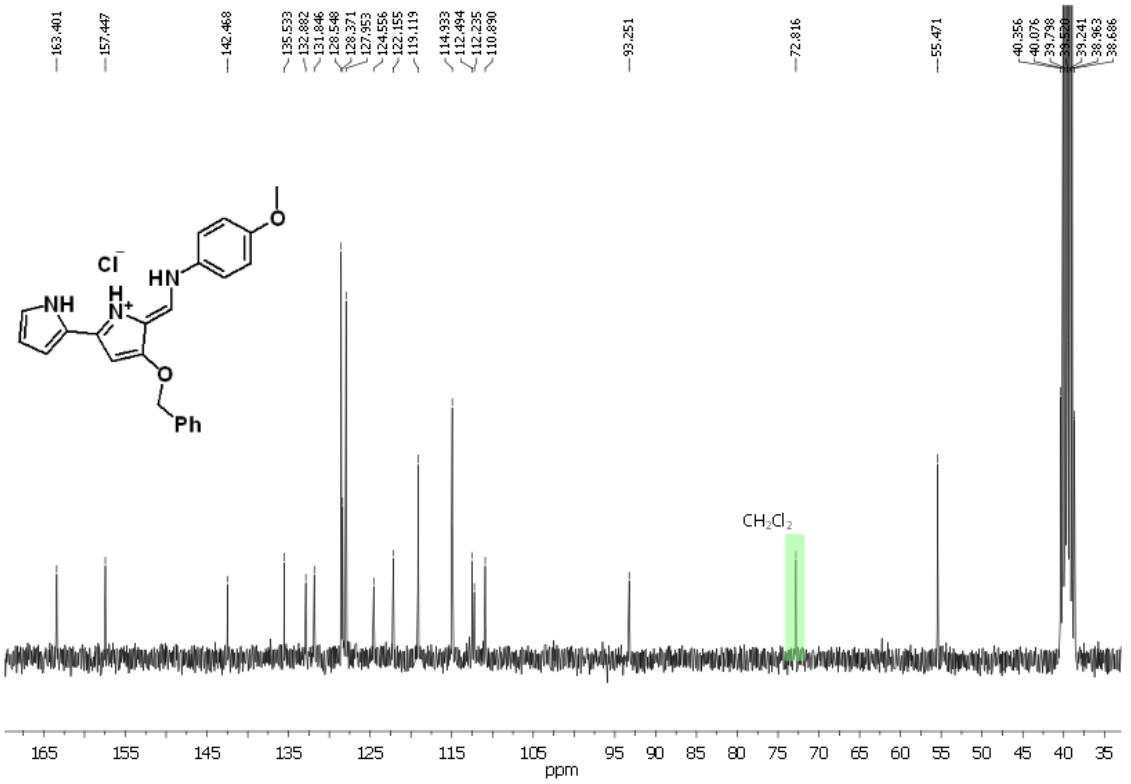

Figure S32. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **9**. HCl.

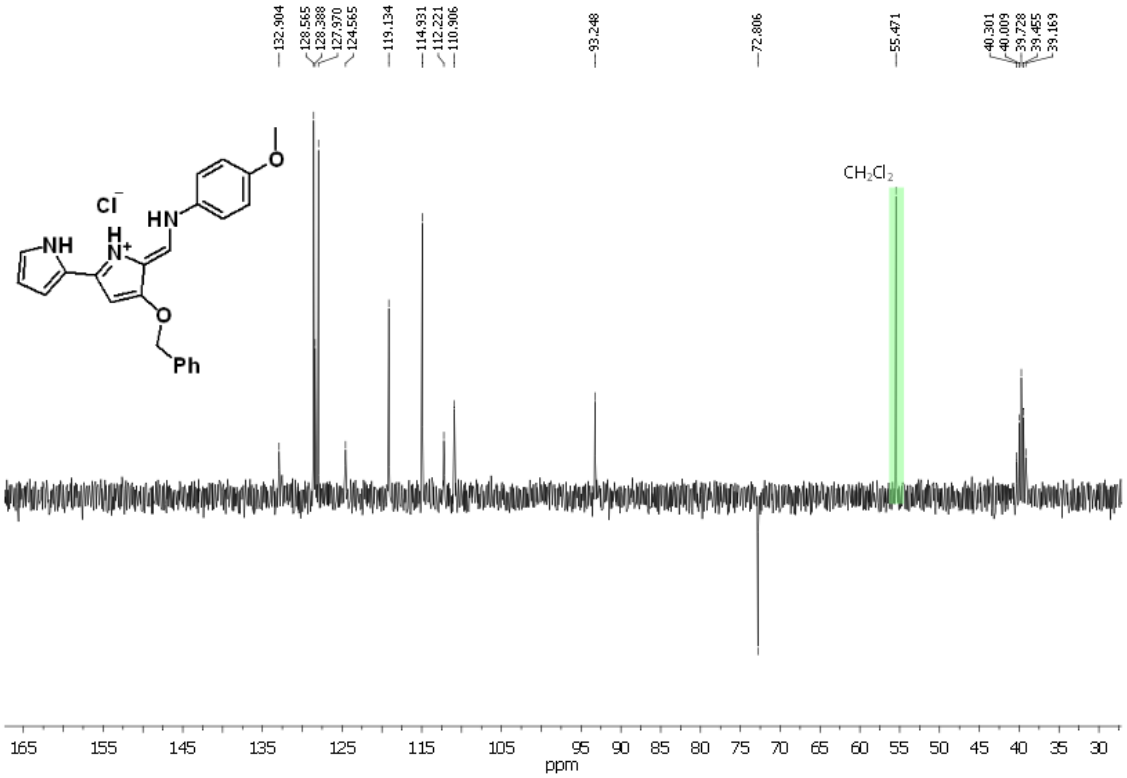

Figure S33. DEPT^{13}C NMR ($CDCl_3$, 75 MHz) of compound **9**. HCl.

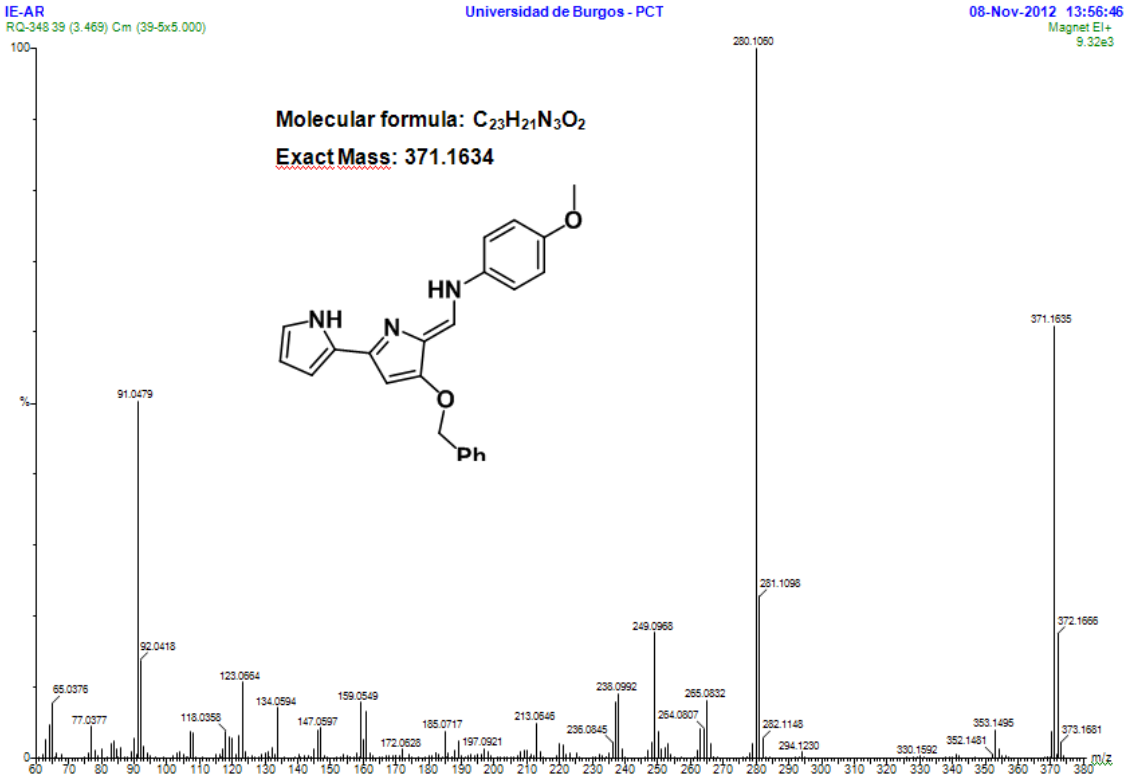

Figure S34. HRMS (EI) of compound **9**.

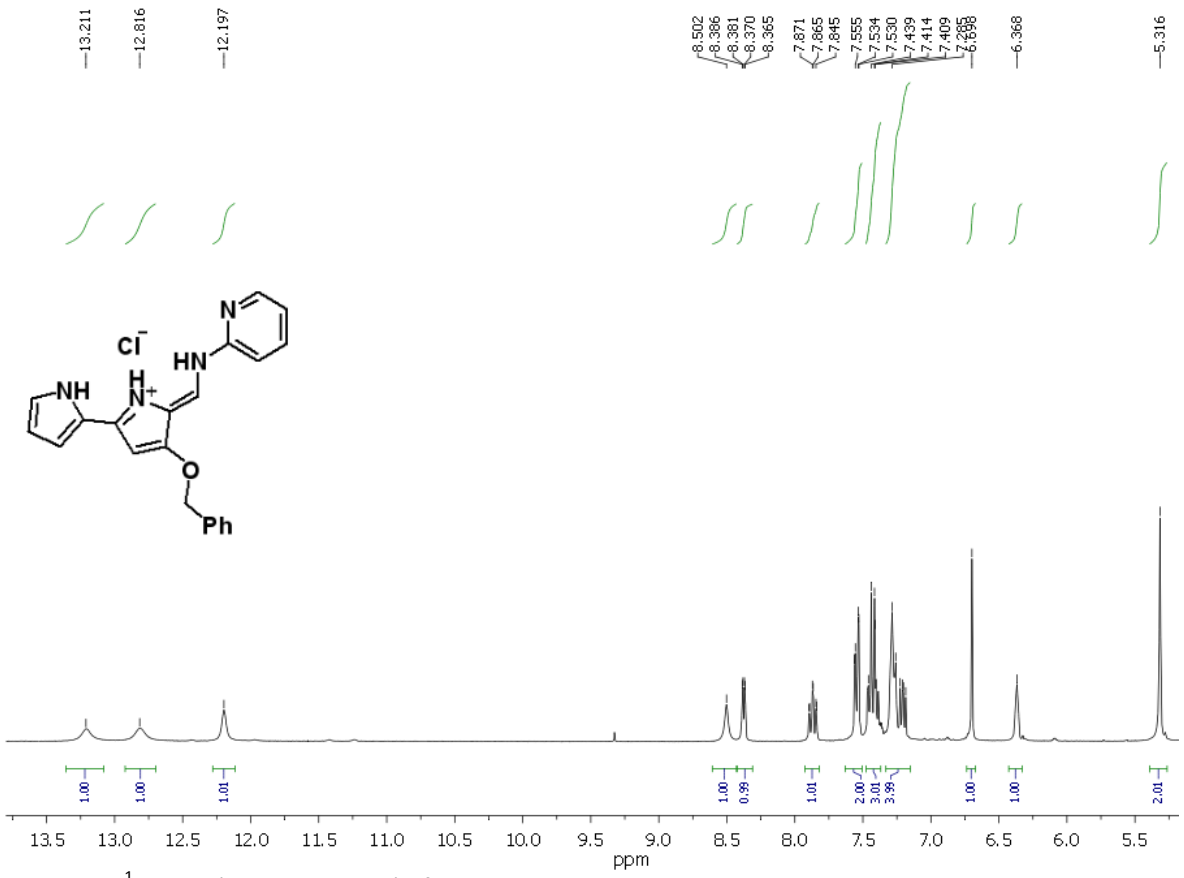

Figure S35. ^{1}H NMR ($CDCl_3$, 300 MHz) of compound **10**. HCl.

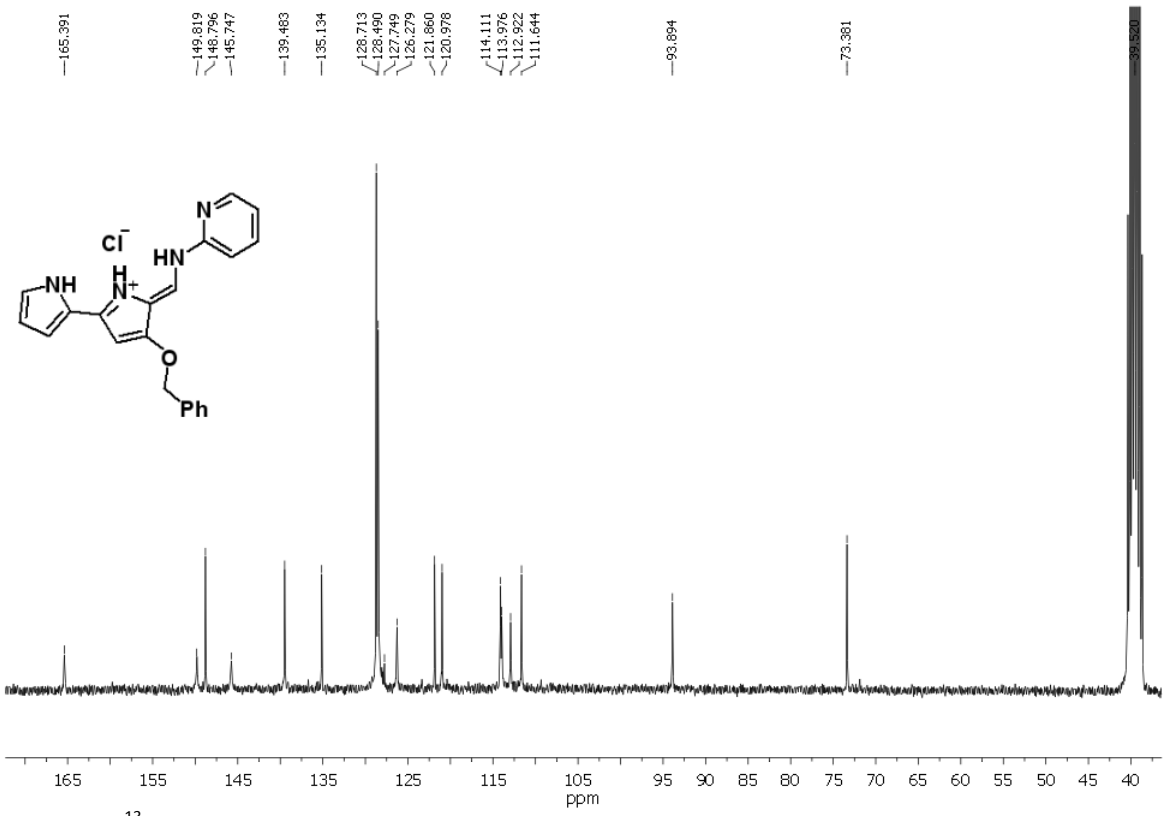

Figure S36. ^{13}C NMR ($CDCl_3$, 75 MHz) of compound **10**. HCl.

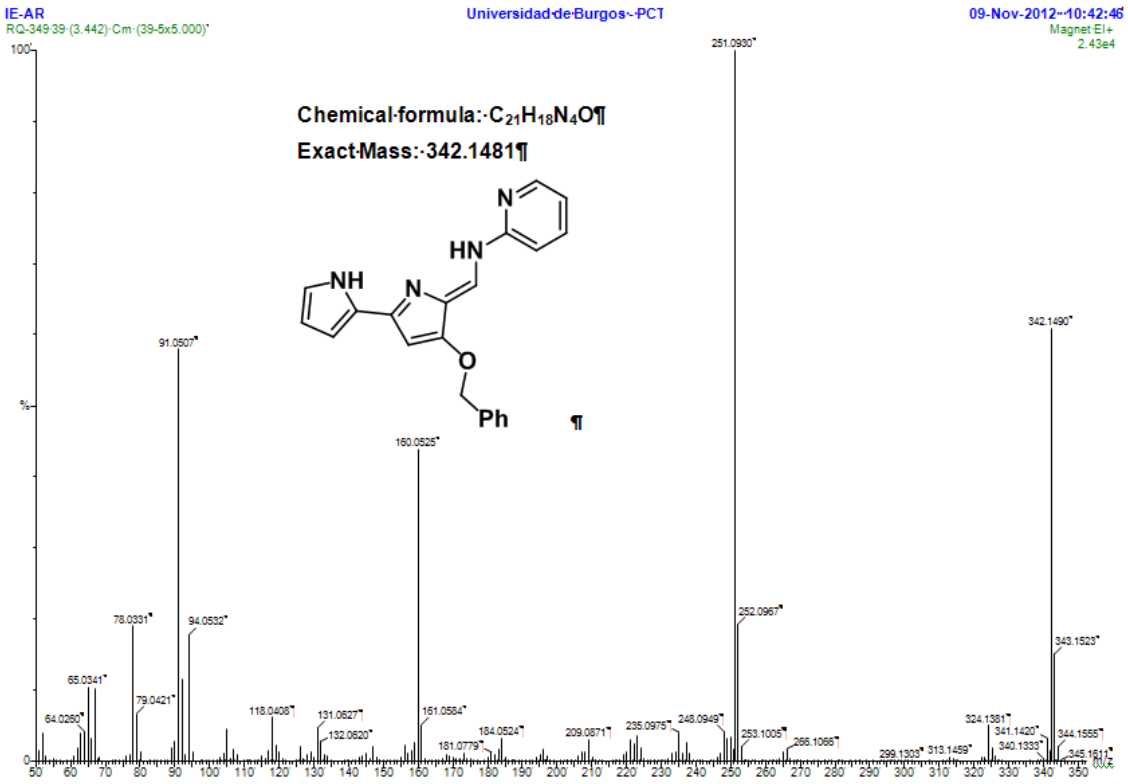

Figure S37. HRMS (EI) of compound **10**.

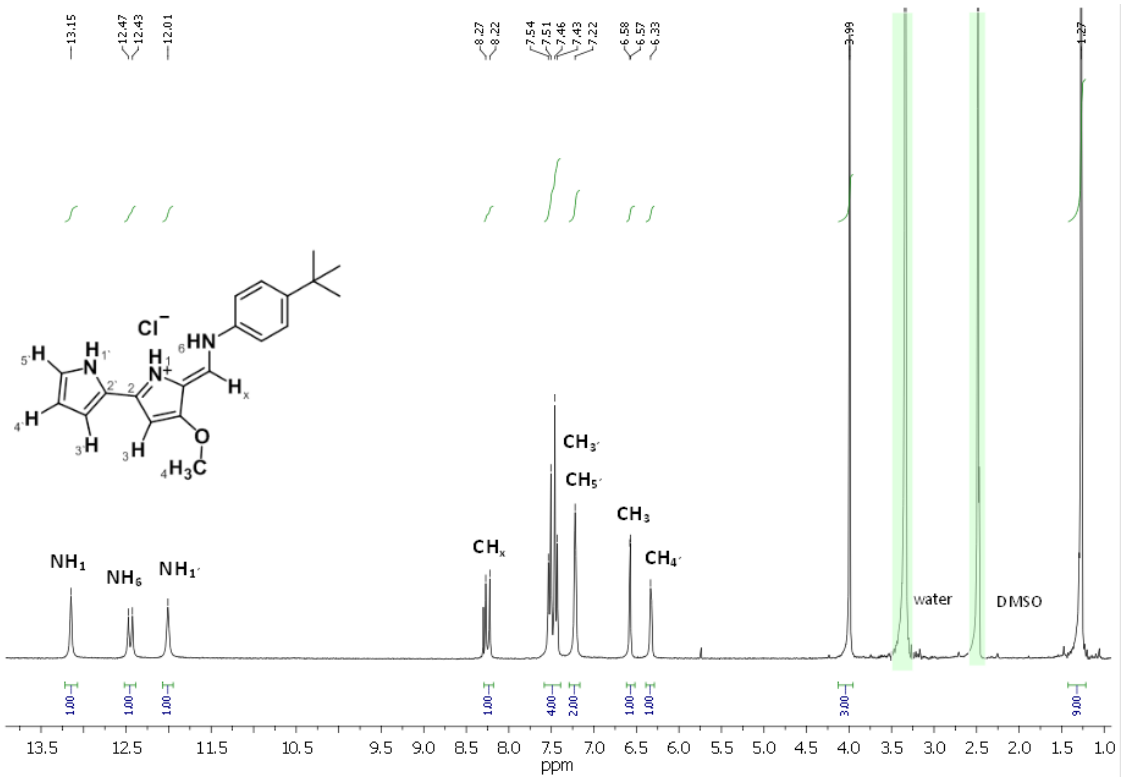

Figure S38. ^{1}H NMR (DMSO-d_6, 300 MHz) of compound **2**. HCl.

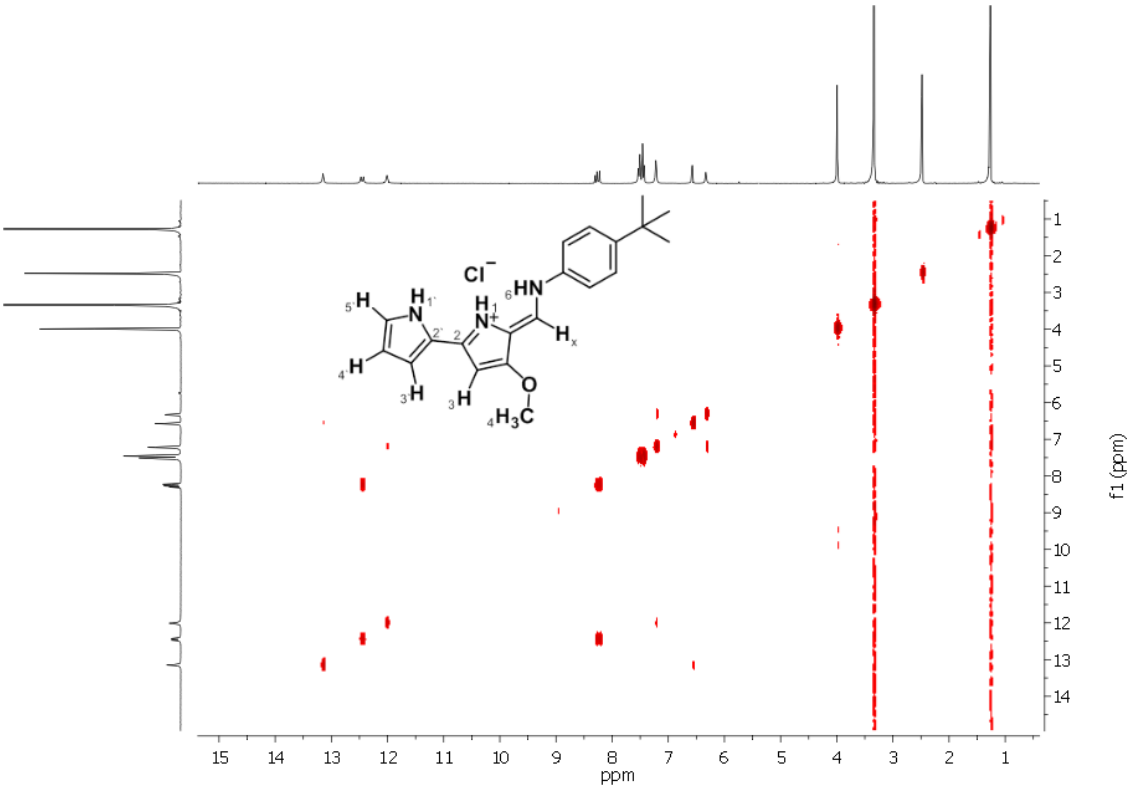

Figure S39. COSY (DMSO-d_6) of compound **2**. HCl.

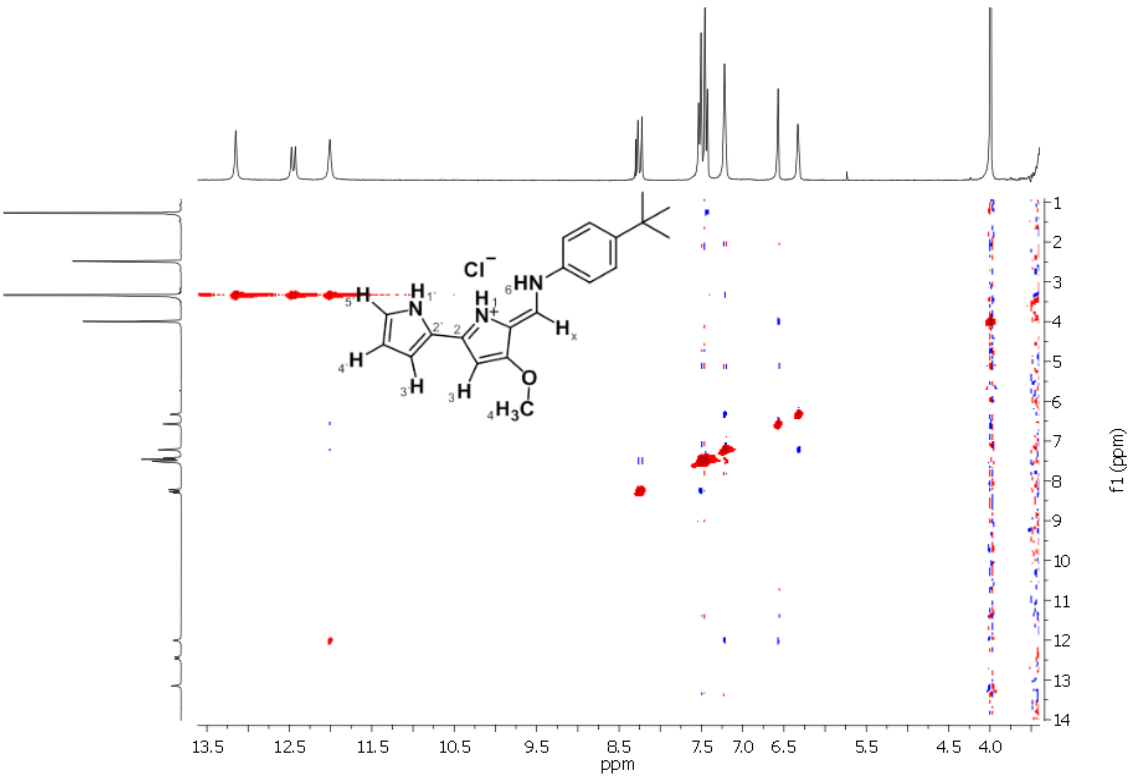

Figure S40. NOESY (DMSO-d_6) of compound **2**. HCl.

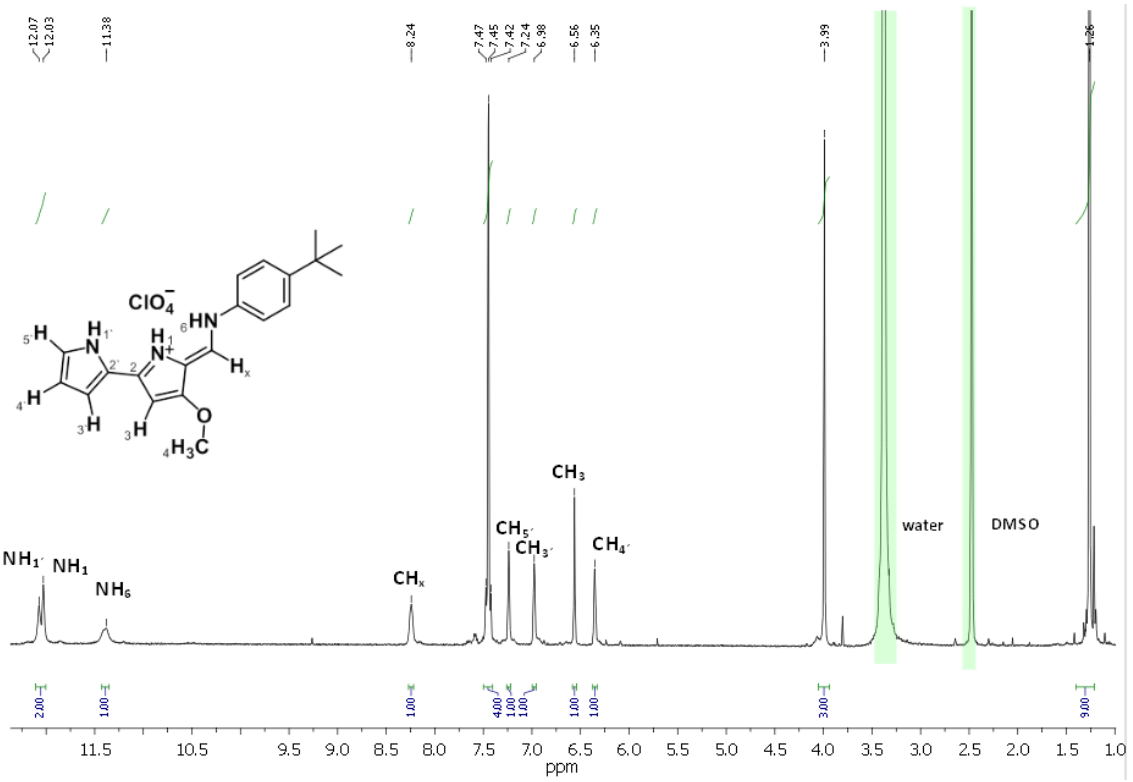

Figure S41. ^{1}H NMR (DMSO-d_6) of compound **2**. $HClO_4$.

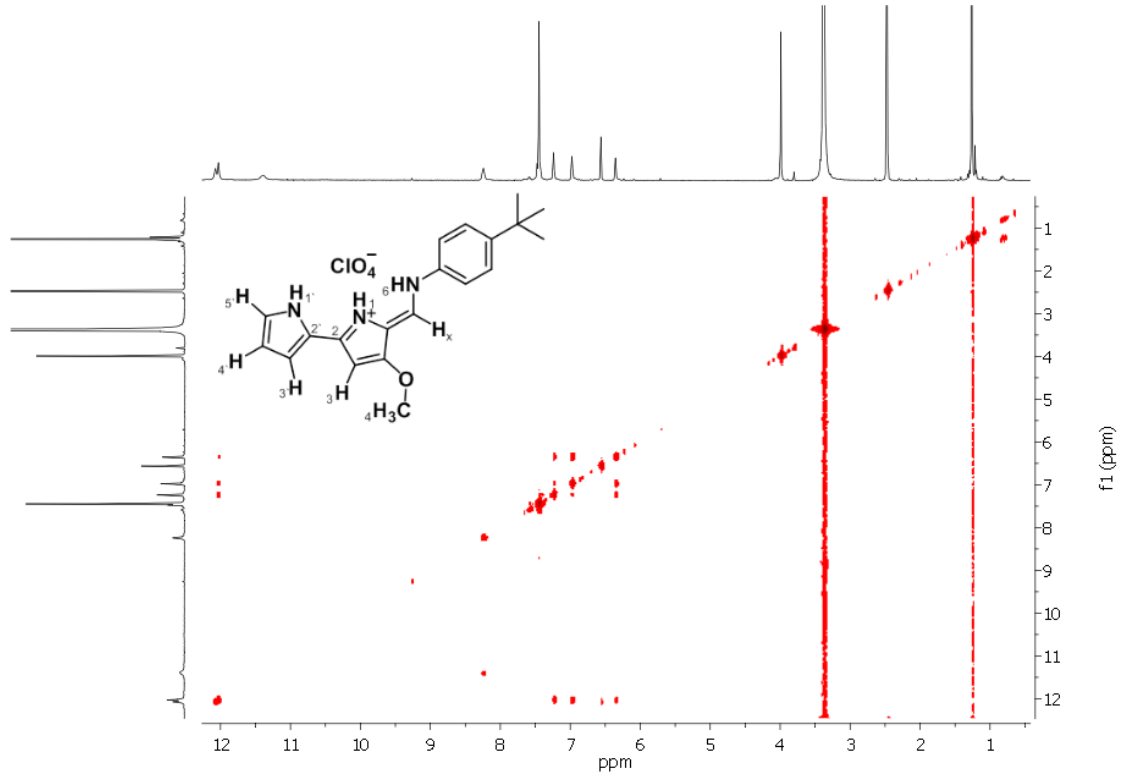

Figure S42. COSY (DMSO-d_6) of compound **2**. $HClO_4$.

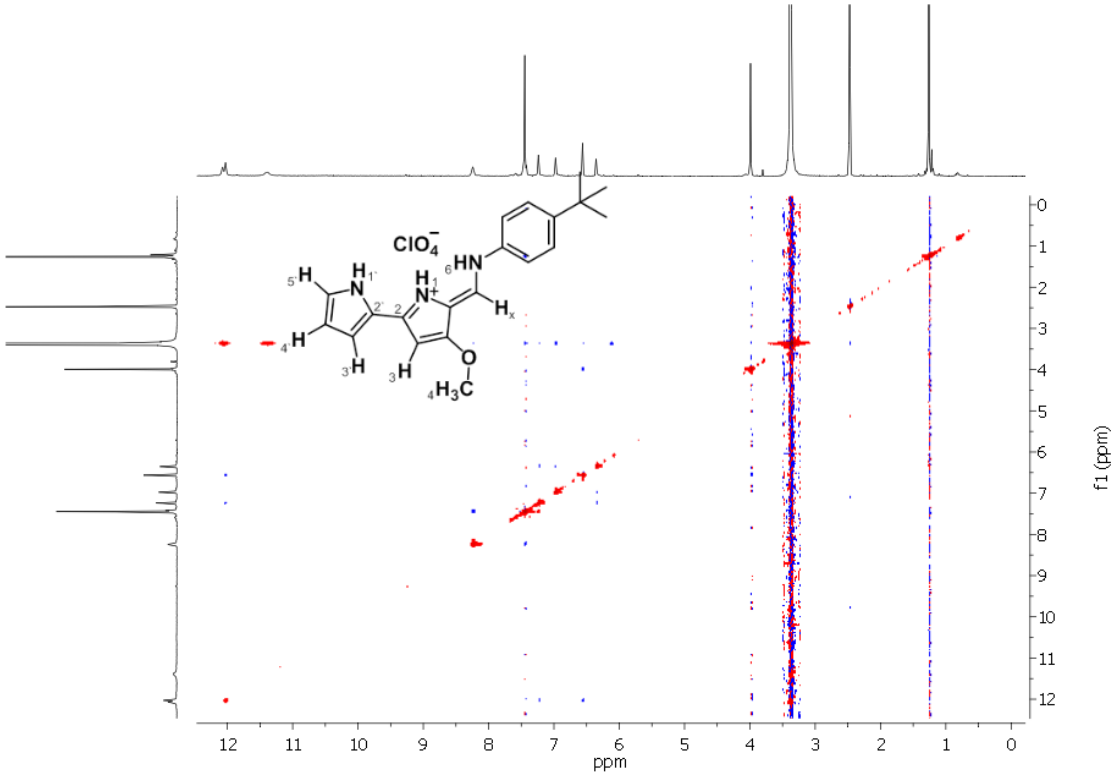

Figure S43. NOESY (DMSO-d_6) of compound **2**. $HClO_4$.

^{1}H NMR titration experiments

In order to estimate the association constants in solution the perchlorate salts of compounds **1**-**10** were prepared by successive treatment the dichloromethane solutions of crude reaction mixtures (acetate salts of the corresponding tambjamine derivatives) with diluted $HClO_4$ (three times). ^{1}H NMR titration experiments were carried out in DMSO-d_6/0.5% H_2O in a Varian Mercury-300 MHz spectrometer. Briefly, a 5 mM host solution was prepared. This solution was used to prepare a TBACl stock solution of 75 mM concentration in chloride. Addition of increasing volumes of this TBACl stock solution to a 0.5 mL NMR sample of host solution were carried out with a micro syringe. A ^{1}H NMR spectrum was measured after each addition. The data obtained were analyzed using the EQWinNMR2 software,[1] by fitting to a 1:1 binding isotherm and the association constants were calculated.

[1] M. J. Hynes, *J. Chem. Soc. Dalton Trans.*, 1993, 311.

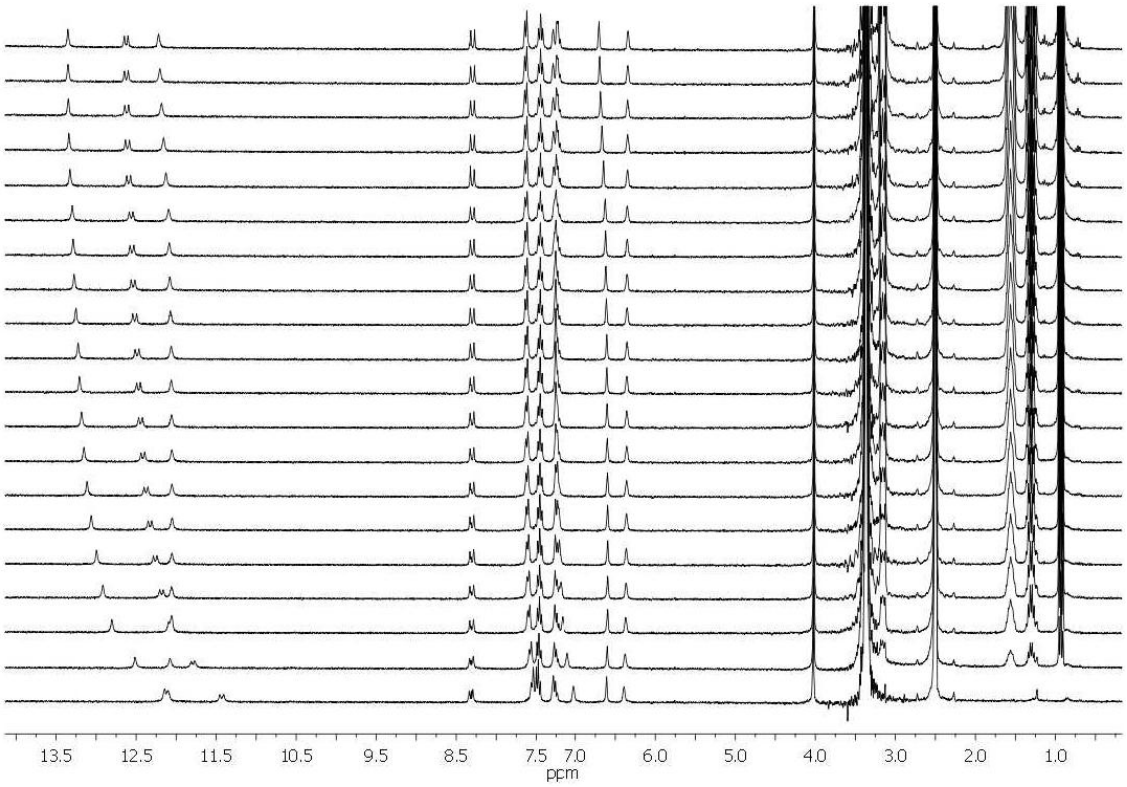

Figure S44. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **1**.$HClO_4$ upon addition of increasing ammounts of TBACl.

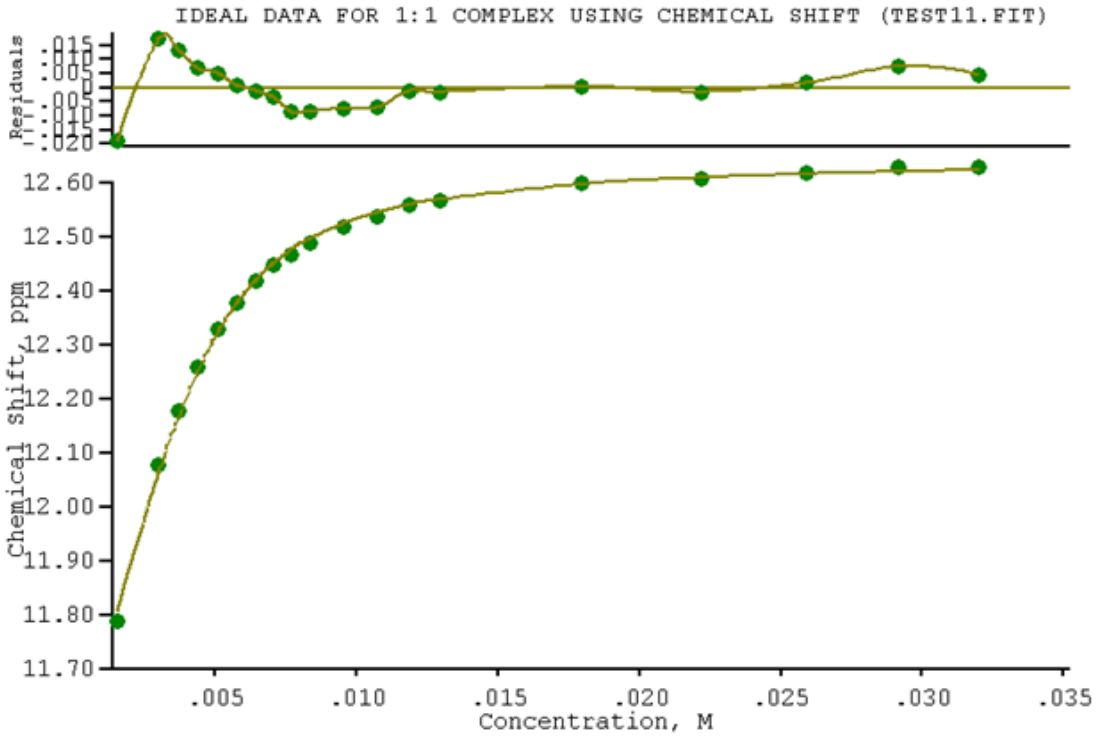

Figure S45. Changes in the chemical shift corresponding to NH_6 of compound **1** (Figure S44) are fitted to a 1:1 model using WinEQNMR2. Ka= 1592 (±25) M^{-1}.

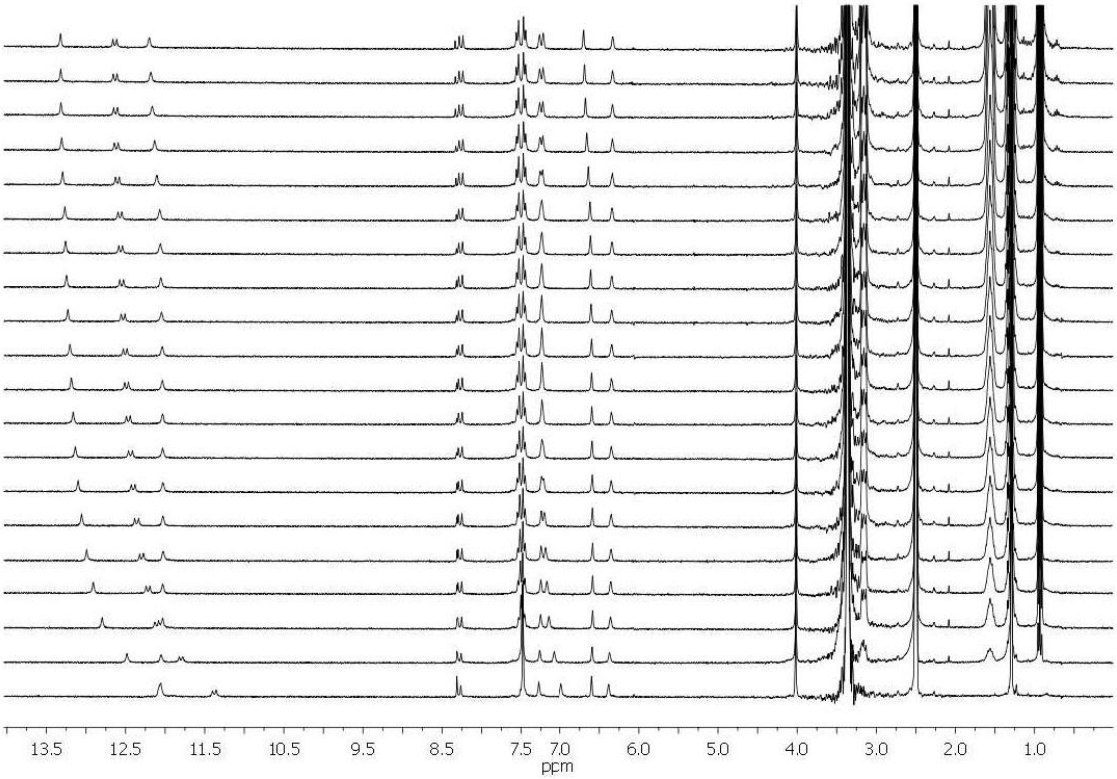

Figure S46. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **2**.$HClO_4$ upon addition of increasing ammounts of TBACl.

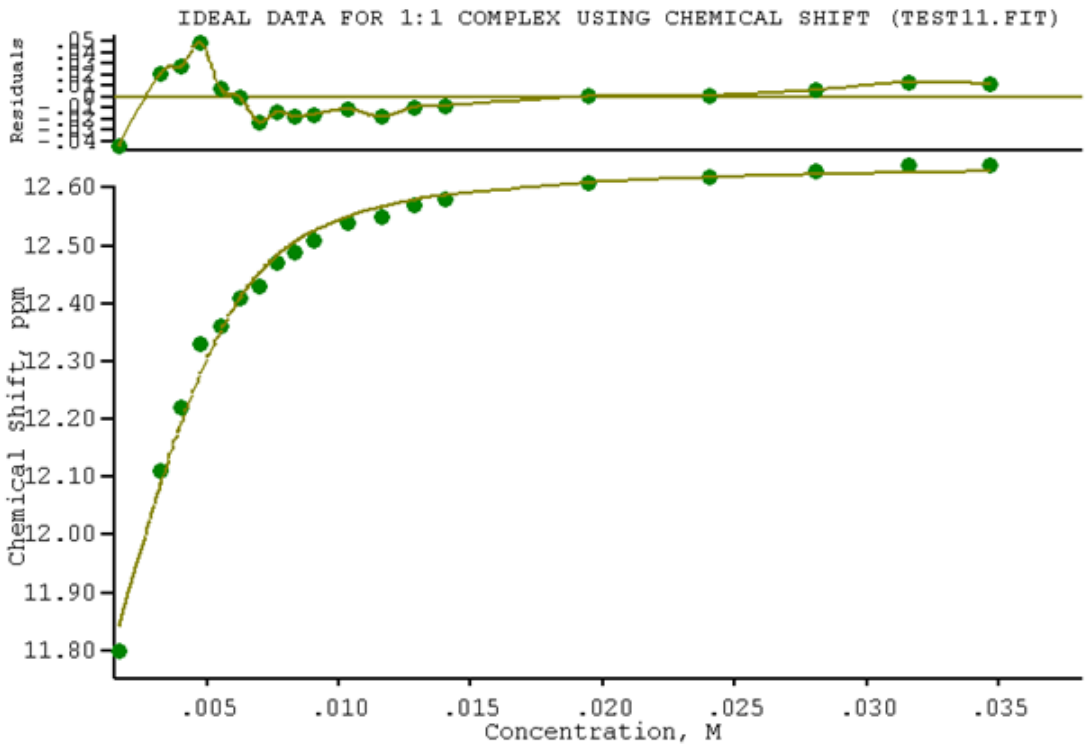

Figure S47. Changes in the chemical shift corresponding to NH_6 of compound **2** (Figure S46) are fitted to a 1:1 model using WinEQNMR2. Ka= 1990 (±122) M^{-1}.

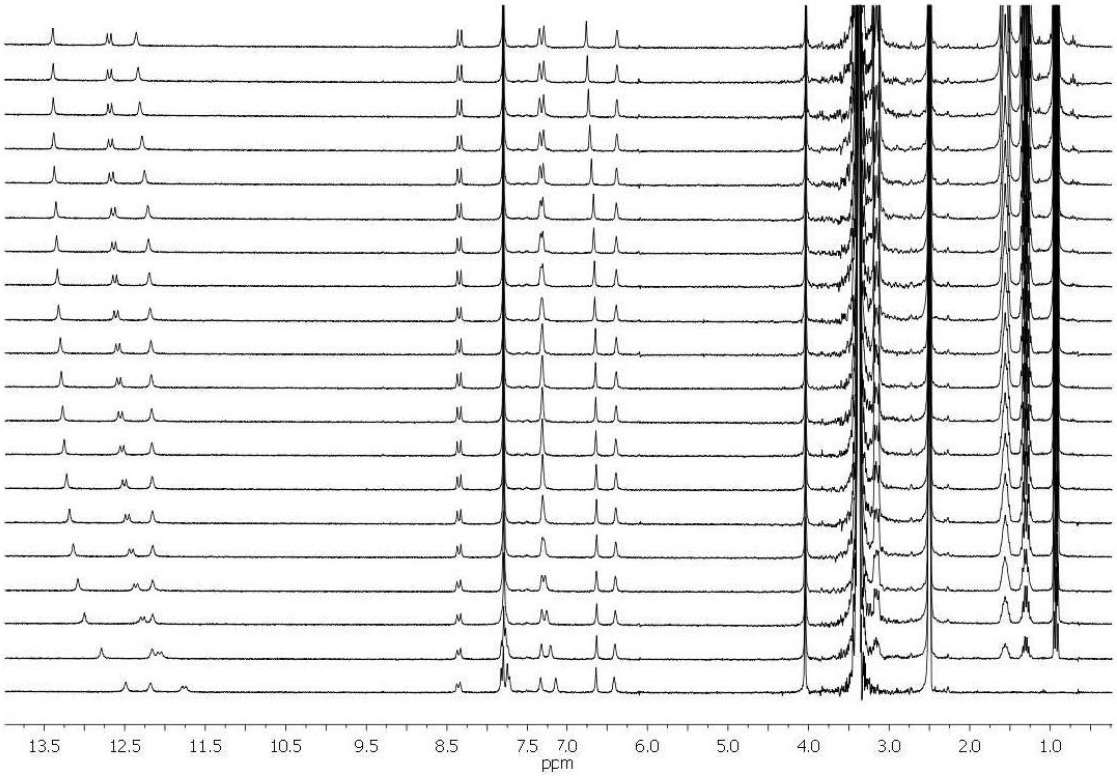

Figure S48. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **3**.$HClO_4$ upon addition of increasing ammounts of TBACl.

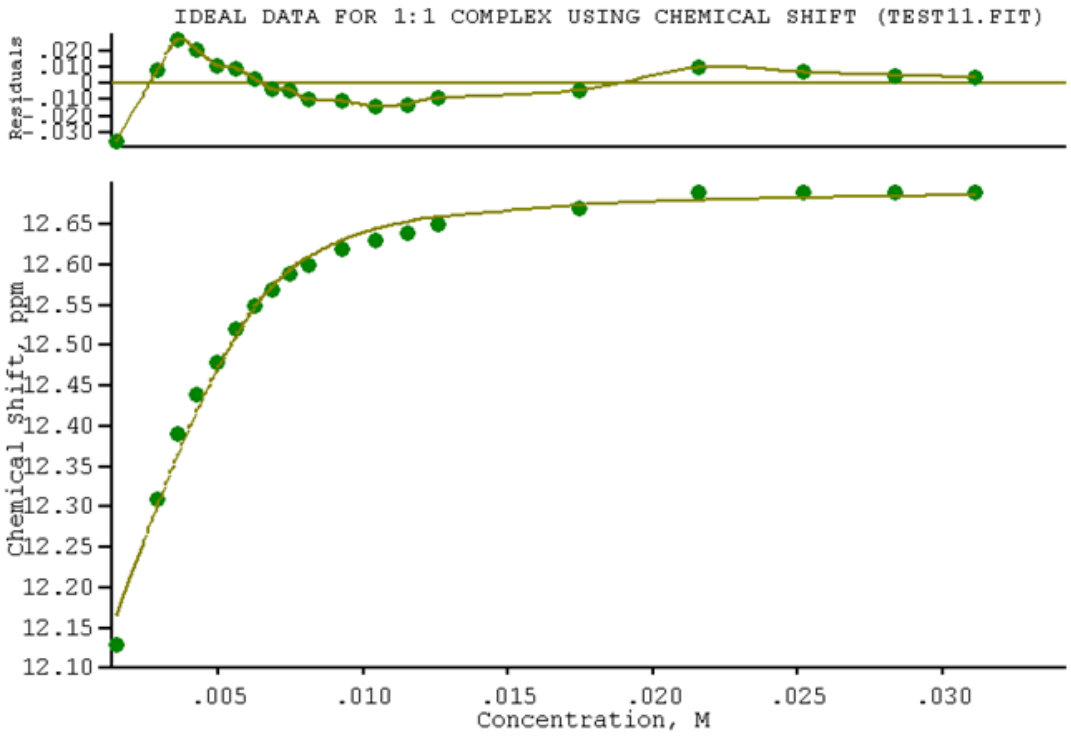

Figure S49. Changes in the chemical shift corresponding to NH_6 of compound **3** (Figure S48) are fitted to a 1:1 model using WinEQNMR2. Ka= 1789 (±222) M^{-1}.

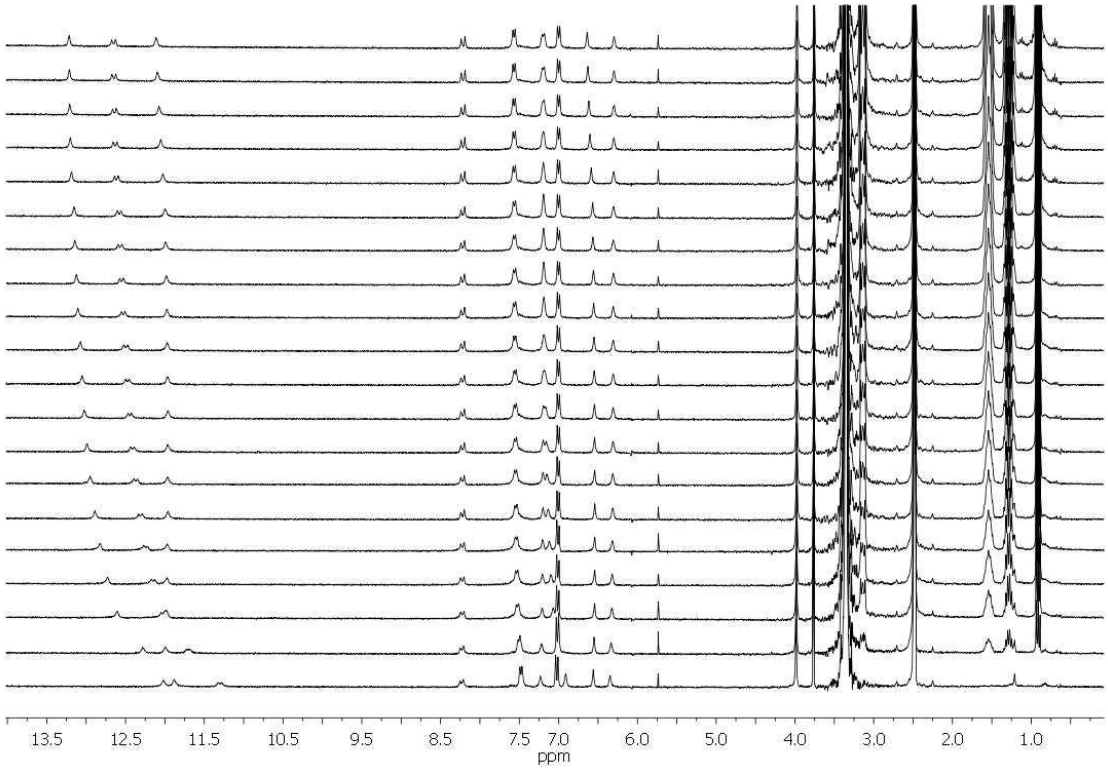

Figure S50. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **4**.$HClO_4$ upon addition of increasing ammounts of TBACl.

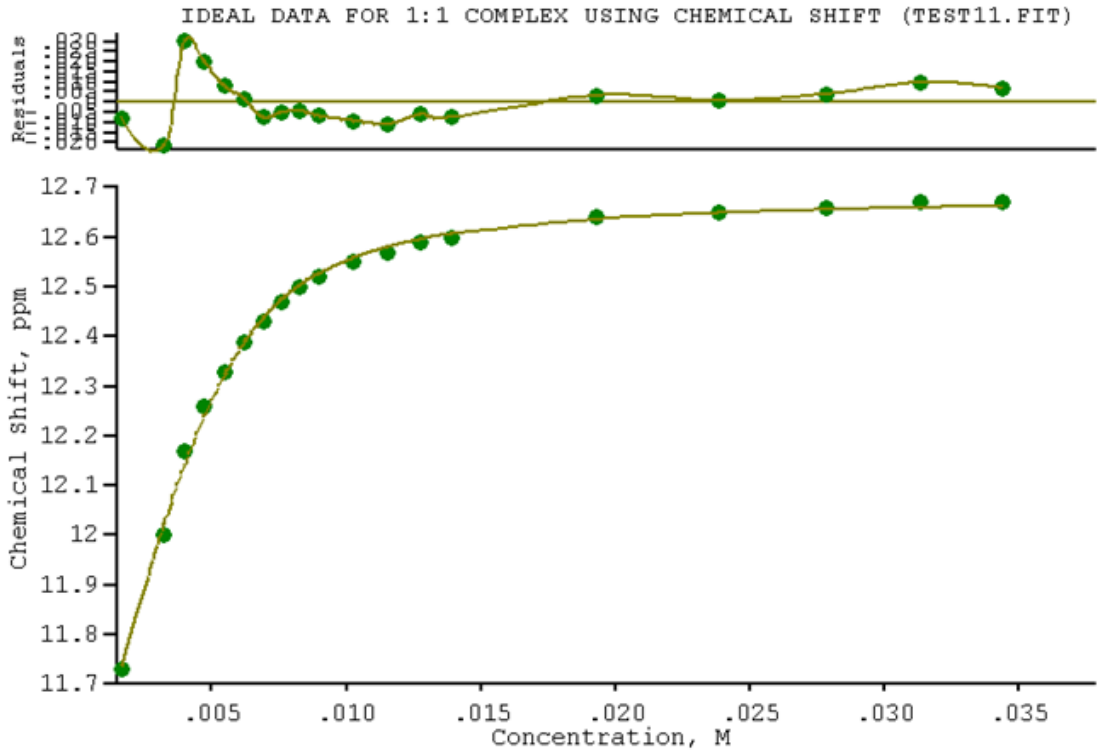

Figure S51. Changes in the chemical shift corresponding to NH_6 of compound **4** (Figure S50) are fitted to a 1:1 model using WinEQNMR2. Ka= 1681 (±107) M^{-1}.

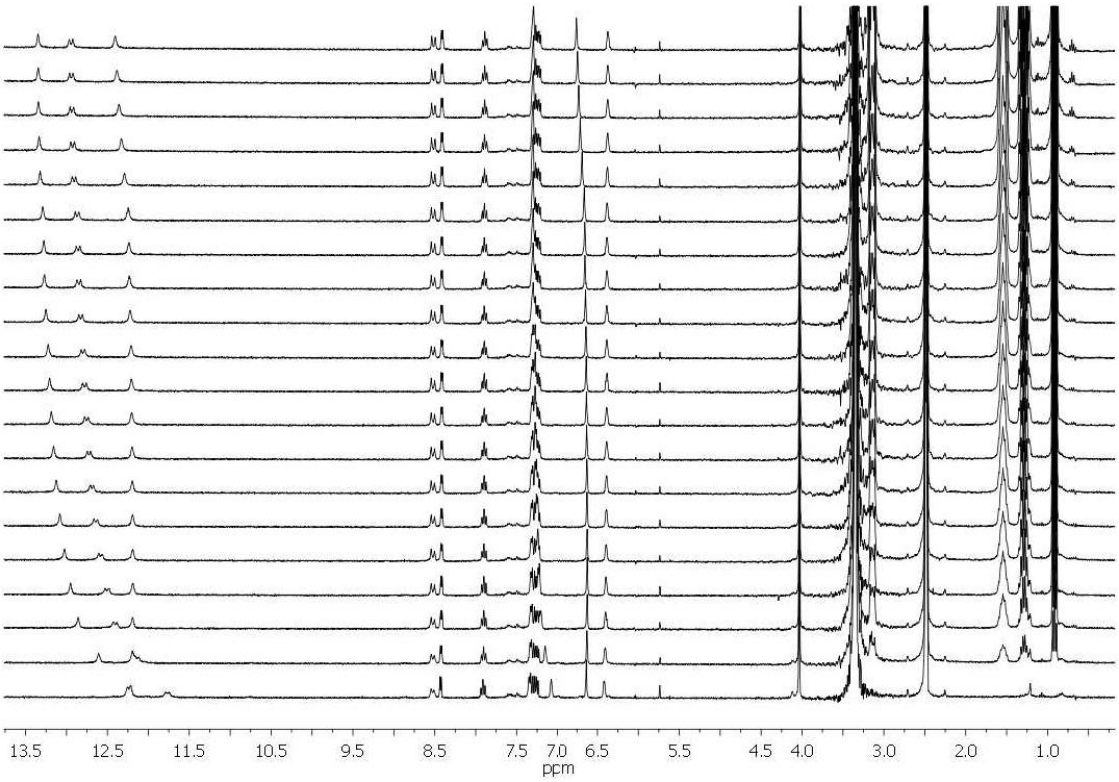

Figure S52. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **5**.$HClO_4$ upon addition of increasing ammounts of TBACl.

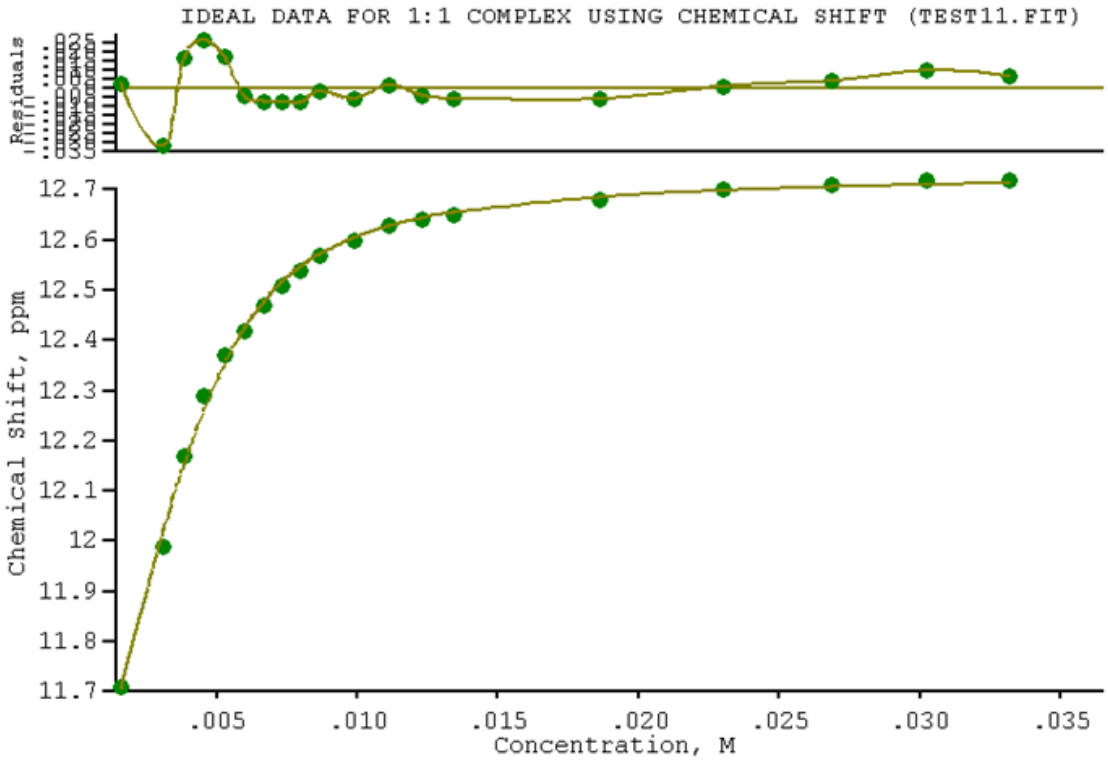

Figure S53. Changes in the chemical shift corresponding to NH_6 of compound **5** (Figure S52) are fitted to a 1:1 model using WinEQNMR2. Ka= 1510 (±157) M^{-1}.

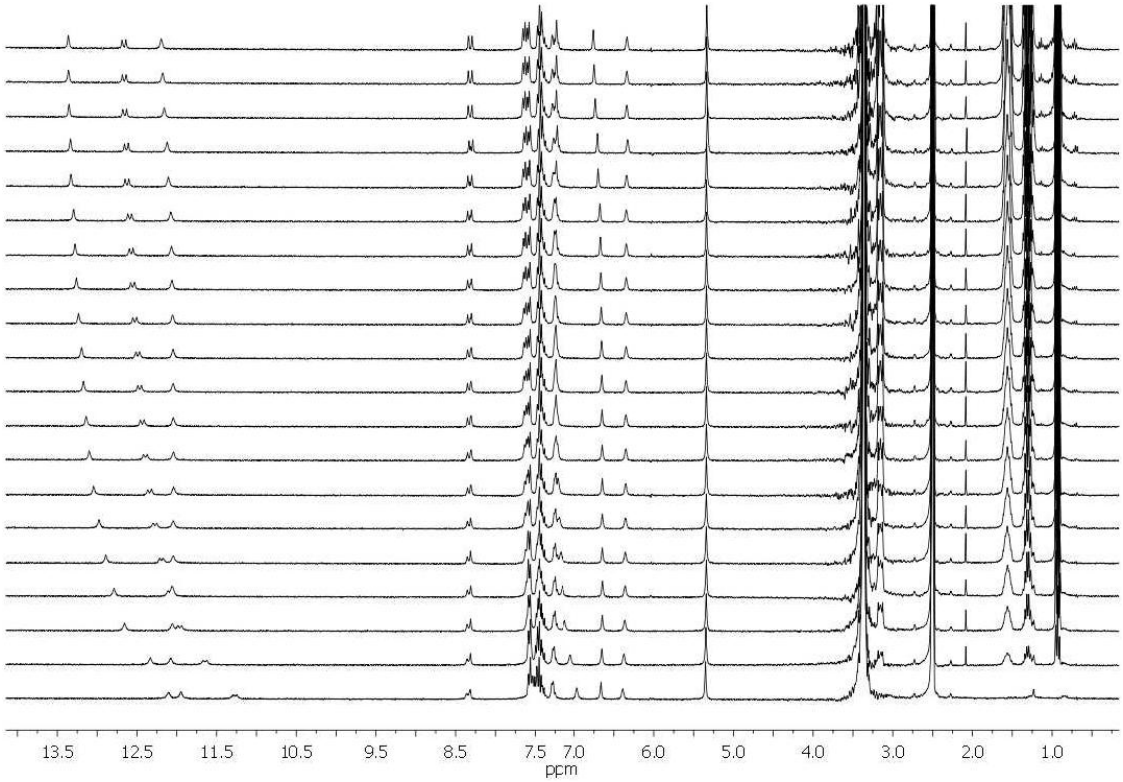

Figure S54. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **6**.$HClO_4$ upon addition of increasing ammounts of TBACl.

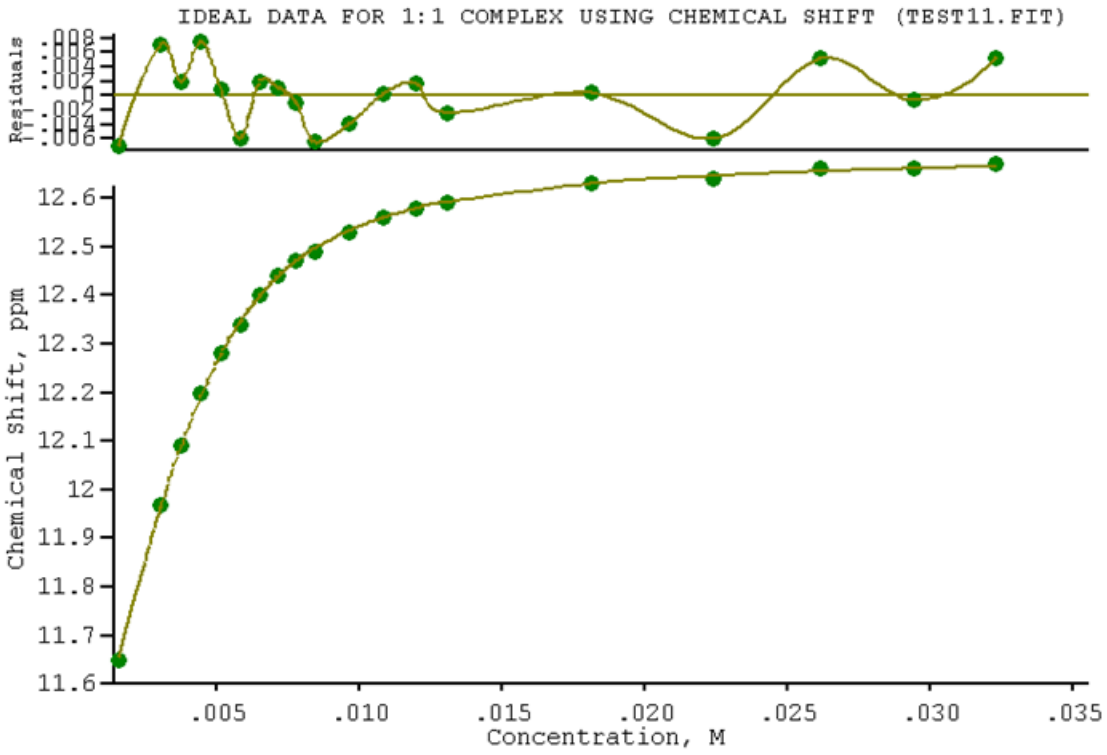

Figure S55. Changes in the chemical shift corresponding to NH_6 of compound **6** (Figure S54) are fitted to a 1:1 model using WinEQNMR2. Ka= 1428 (±30) M^{-1}.

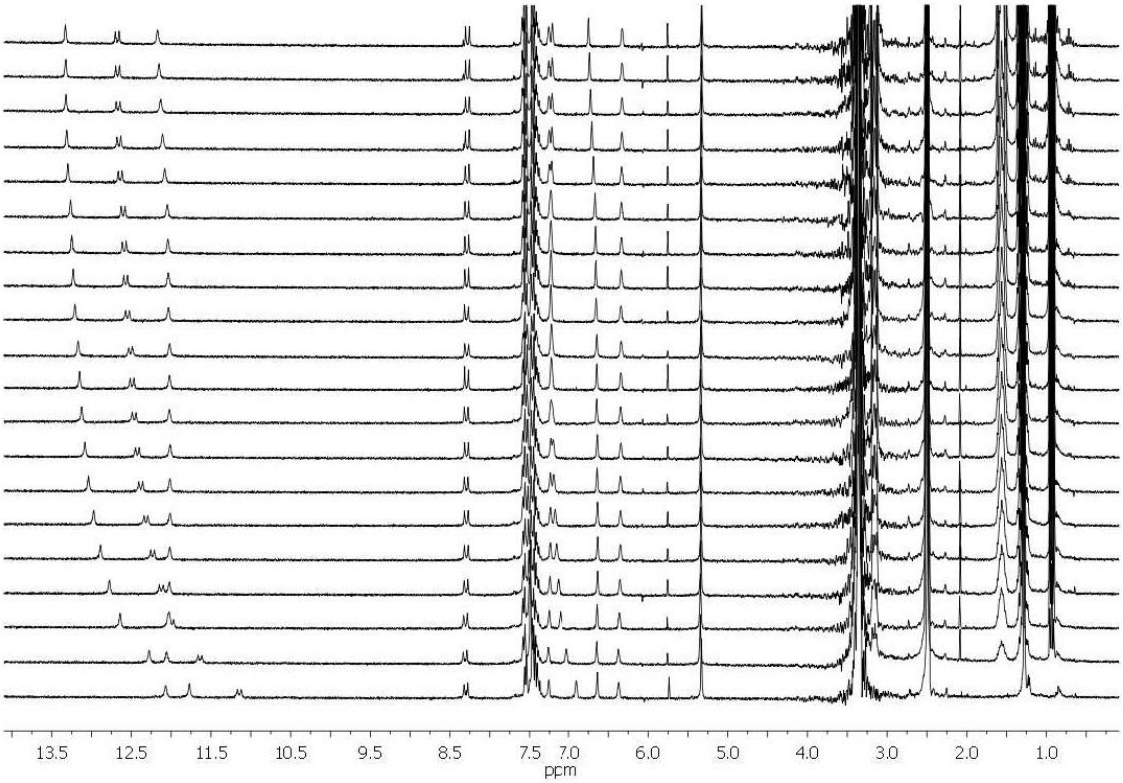

Figure S56. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **7**.$HClO_4$ upon addition of increasing ammounts of TBACl.

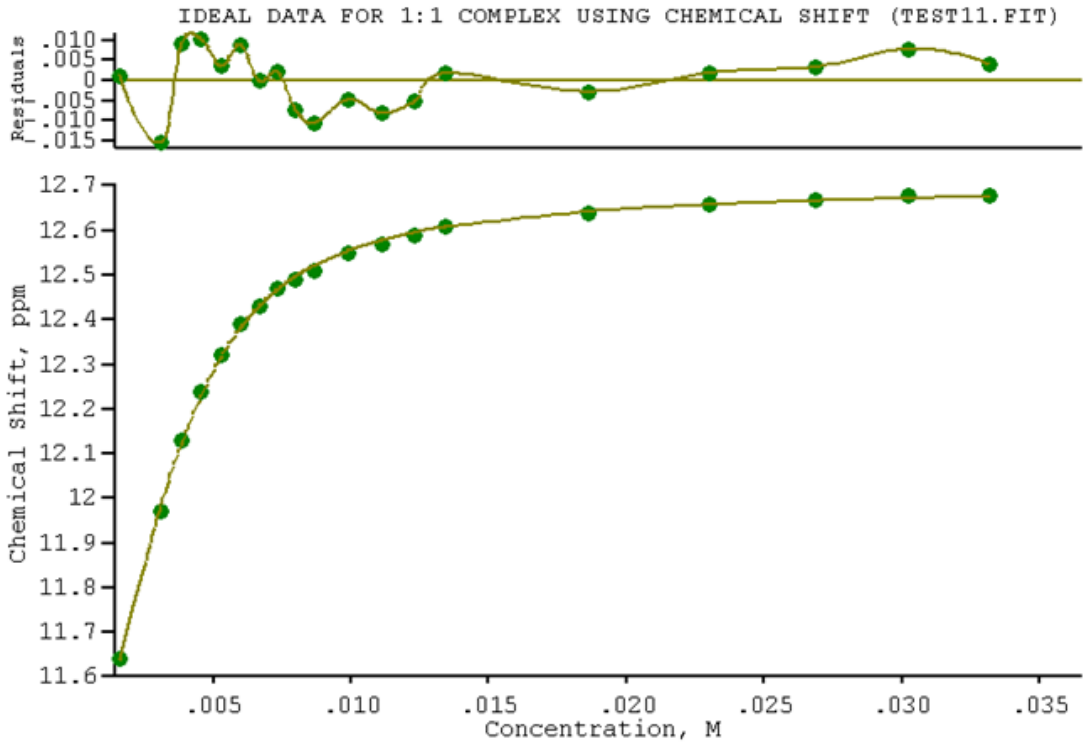

Figure S57. Changes in the chemical shift corresponding to NH_6 of compound **7** (Figure S56) are fitted to a 1:1 model using WinEQNMR2. Ka= 1498 (±48) M^{-1}.

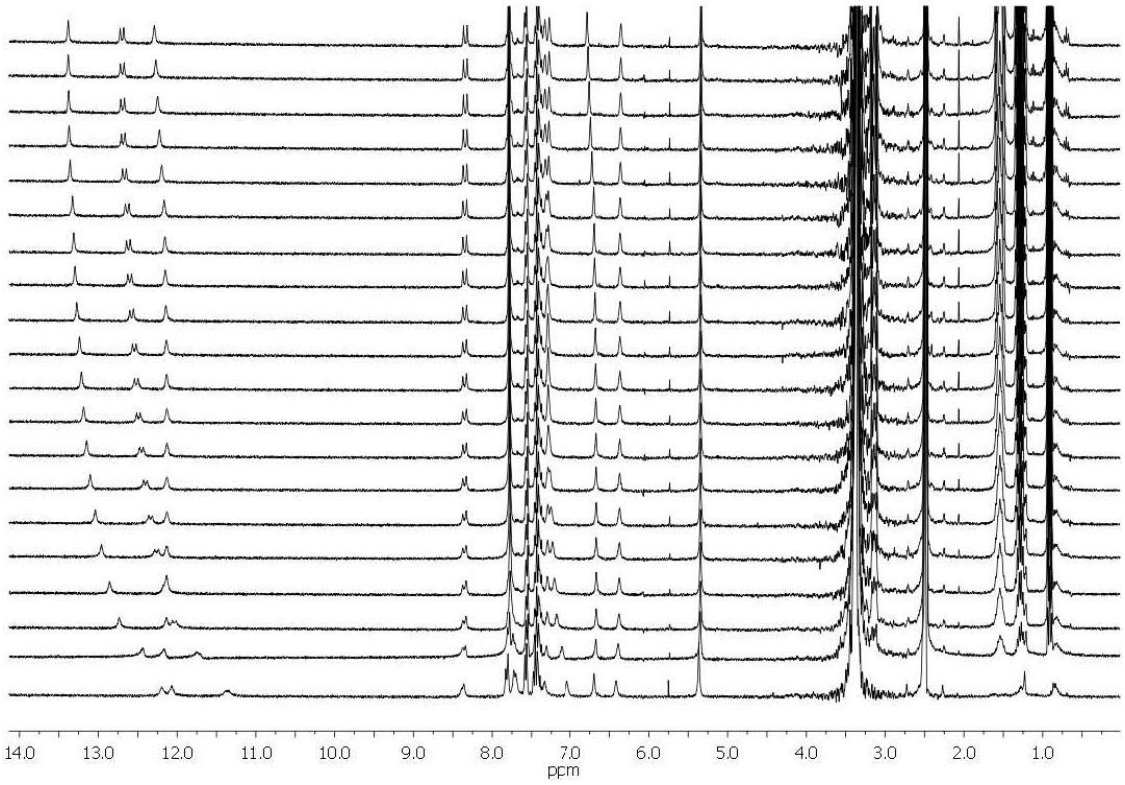

Figure S58. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **8**.$HClO_4$ upon addition of increasing ammounts of TBACl.

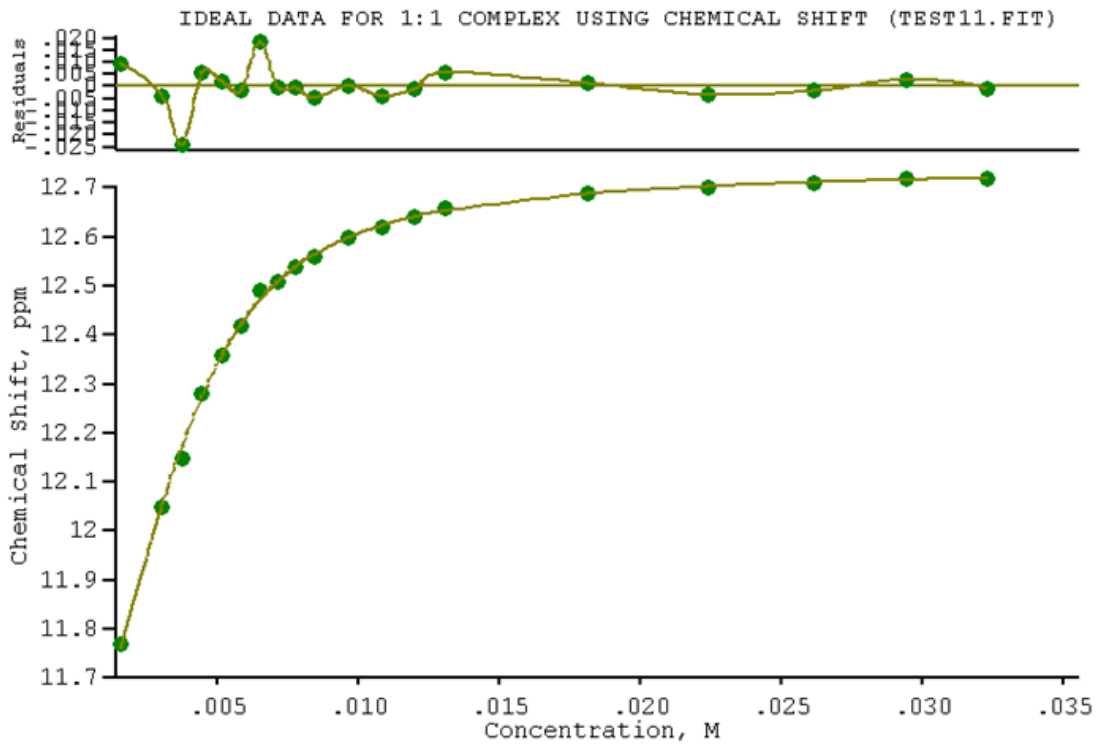

Figure S59. Changes in the chemical shift corresponding to NH_6 of compound **8** (Figure S58) are fitted to a 1:1 model using WinEQNMR2. Ka= 1491 (±59) M^{-1}.

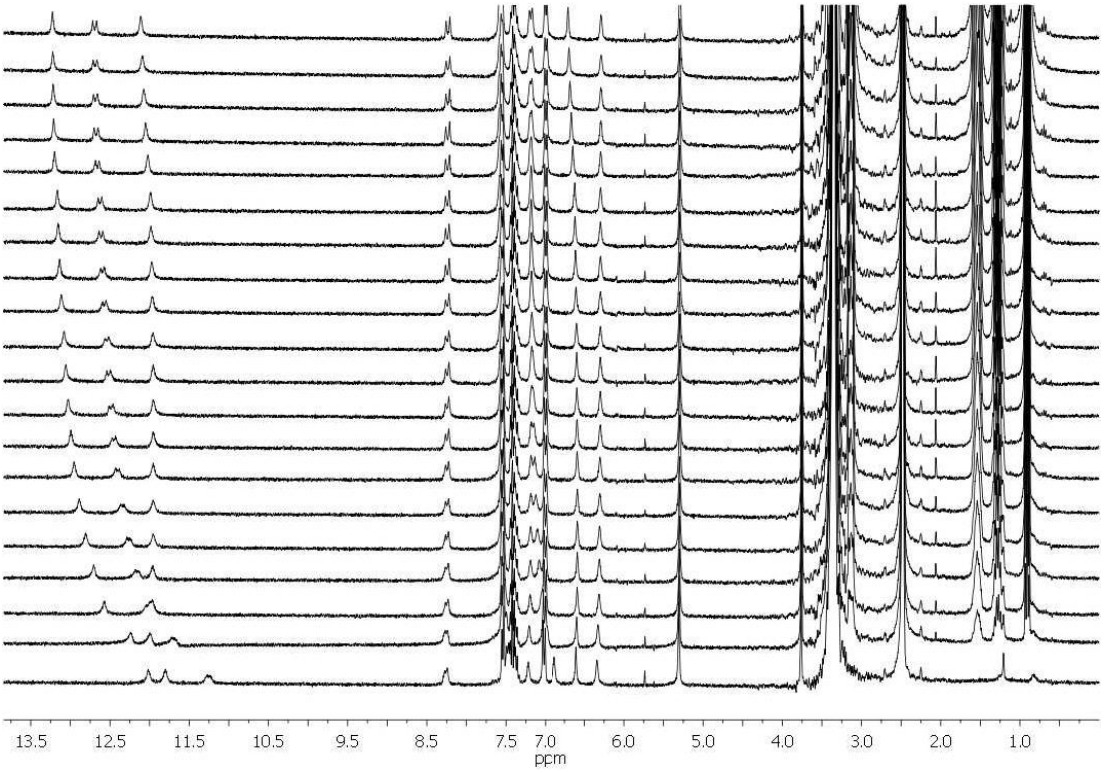

Figure S60. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **9**.$HClO_4$ upon addition of increasing ammounts of TBACl.

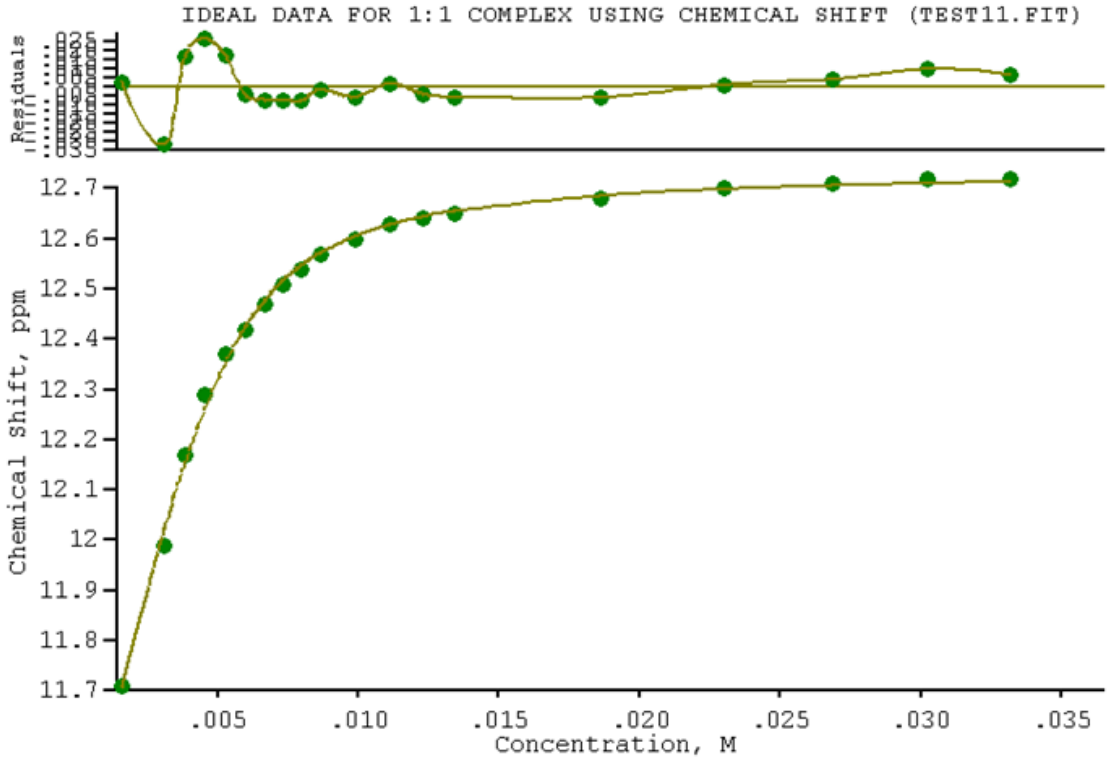

Figure S61. Changes in the chemical shift corresponding to NH_6 of compound **9** (Figure S60) are fitted to a 1:1 model using WinEQNMR2. Ka= 1836 (±114) M^{-1}.

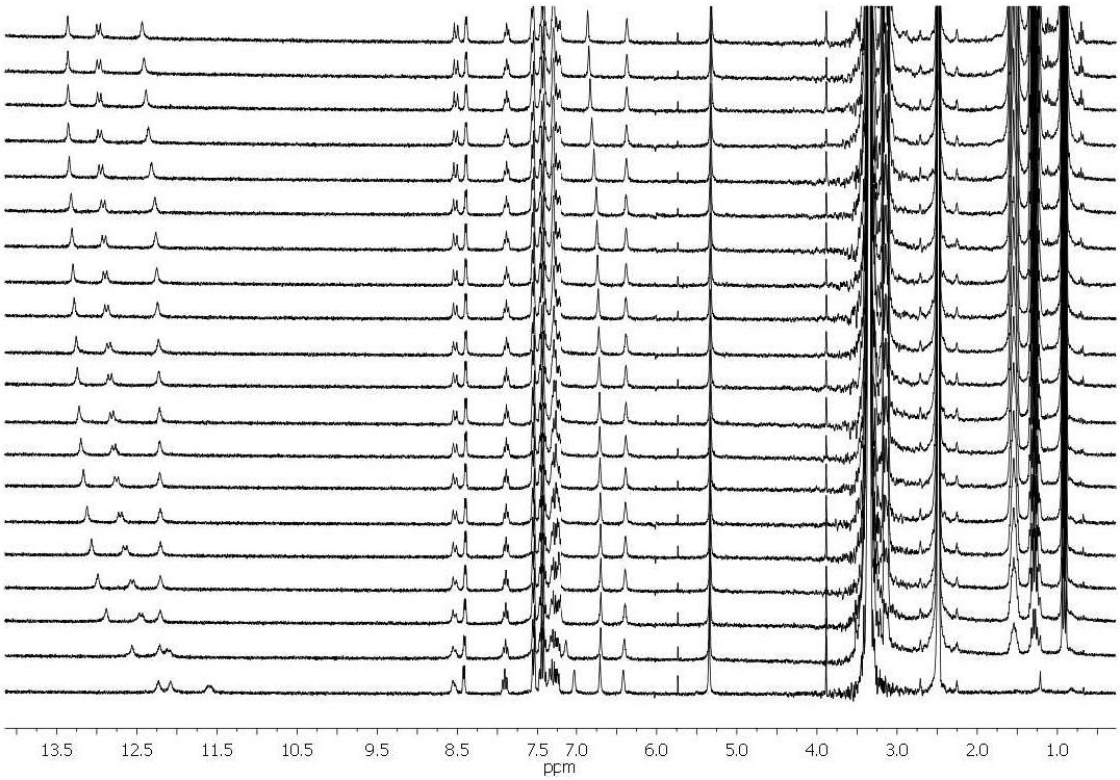

Figure S62. Stack plot of ^{1}H-NMR ($CDCl_3$, 300MHz) of compound **10**.$HClO_4$ upon addition of increasing ammounts of TBACl.

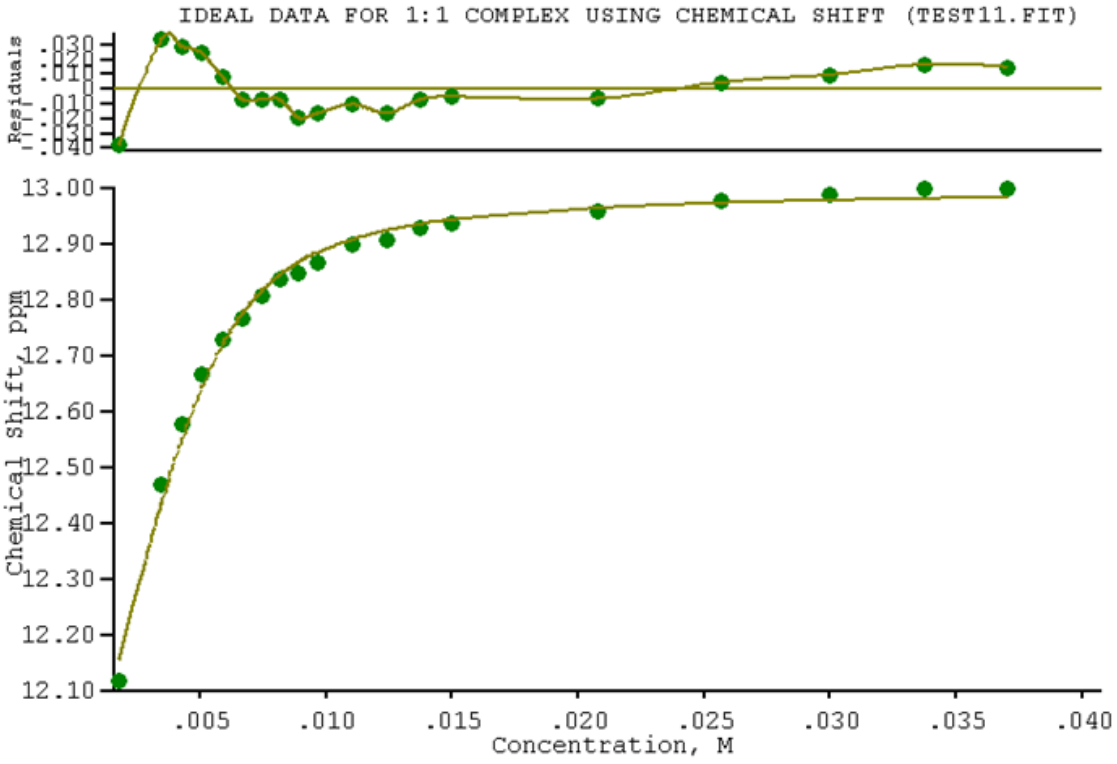

Figure S63. Changes in the chemical shift corresponding to NH_6 of compound **10** (Figure S62) are fitted to a 1:1 model using WinEQNMR2. Ka= 1960 (±219) M^{-1}.

Lipophilicity calculations

LogP (the octanol/water partition coefficient) is the most commonly used parameter for estimating the lipophilicity of a compound. logP values for compounds 1-10 were calculated usig the VCCLab software.[2] This software provides a consensus LogP as the average of LogP values calculated from substructure based methods and properties based methods. We have previously demonstrated that these values correlate well with the retention times on reverse HPLC columns for this type of derivatives, an experimental estimation of the lipophilicity of compounds.[3] Likewise we showed that there is a linear correlation between calculated logP for the different tautomeric forms of tambjamine derivatives using this software.

Table S1 Calculated LogP values for compounds **1**-**10**.

Compound	Average LogP
1	2,53
2	4,13
3	3,37
4	2,44
5	1,94
6	4,05
7	5,58
8	4,86
9	3,94
10	3,43

[2] (a) I. V. Tetko, J. Gasteiger, R. Todeschini, A. Mauri, D. Livingstone, P. Ertl, V. A. Palyulin, E. V. Radchenko, N. S. Zefirov, A. S. Makarenko, V. Y. Tanchuk, V. V. Prokopenko, *Comput. Aid. Mol. Des.*, **2005**, 19, 453; (b) VCCLAB, Virtual Computational Chemistry Laboratory, http://www.vcclab.org, 2005.

[3] V. Saggiomo, S. Otto, I. Marques, V. Félix, T. Torroba, and R. Quesada, *Chem. Commun.*, 2012, **48**, 5274-5276

Anion transport assays

Table S2 Overview of transport activities expressed as EC_{50} (nM and %) for compounds **1**-**10**.

Compound	EC_{50} (μM) NO_3^-/Cl^-	EC_{50} (% molar carrier to lipid) NO_3^-/Cl^-	Hill parameter n NO_3^-/Cl^-	EC_{50} (μM) HCO_3^-/Cl^- [b]	EC_{50} (% molar carrier to lipid) HCO_3^-/Cl^-	Hill parameter n HCO_3^-/Cl	EC_{50} (HCO_3^-/Cl^-)/ EC_{50} (NO_3^-/Cl^-)
1	40 ± 2	7 ± 0. 4	1.17 ± 0.09	460 ± 70	90 ± 10	0.89 ± 0.1	11.5
2	50 ± 8	10 ± 1	1.14 ± 0.3	240 ± 40	50 ± 0.7	1.19 ± 0.2	4.8
3	140 ± 6	30 ± 1	1.18 ± 0.07	890 ± 80	200 ± 20	1.04 ± 0.09	6.4
4	70 ± 5	10 ± 1	1.39 ± 0.2	460 ± 60	90 ± 10	0.90 ± 0.1	6.6
5	20 ± 9	4 ± 3	0.92 ± 0.3	260 ± 30	50 ± 5	1.05 ± 0.08	13
6	80 ± 10	10 ± 3	1.32 ± 0.3	370 ± 50	70 ± 10	1.12 ± 0.2	4.6
7	60 ± 3	10 ± 0.5	1.20 ± 0.09	880 ± 300	200 ± 60	0.67 ± 0.1	14.7
8	720 ± 70	100 ± 10	1.04 ± 0.09	11920 ± 1000	2400 ± 200	1.11 ± 0.1	16.6
9	70 ± 3	13 ± 0.	1.45 ± 0.1	430 ± 100	90 ± 20	0.99 ± 0.1	6.1
10	40 ± 2	9 ± 0.4	1.24 ± 0.1	170 ± 20	30 ± 4	1.10 ± 0.1	4.3

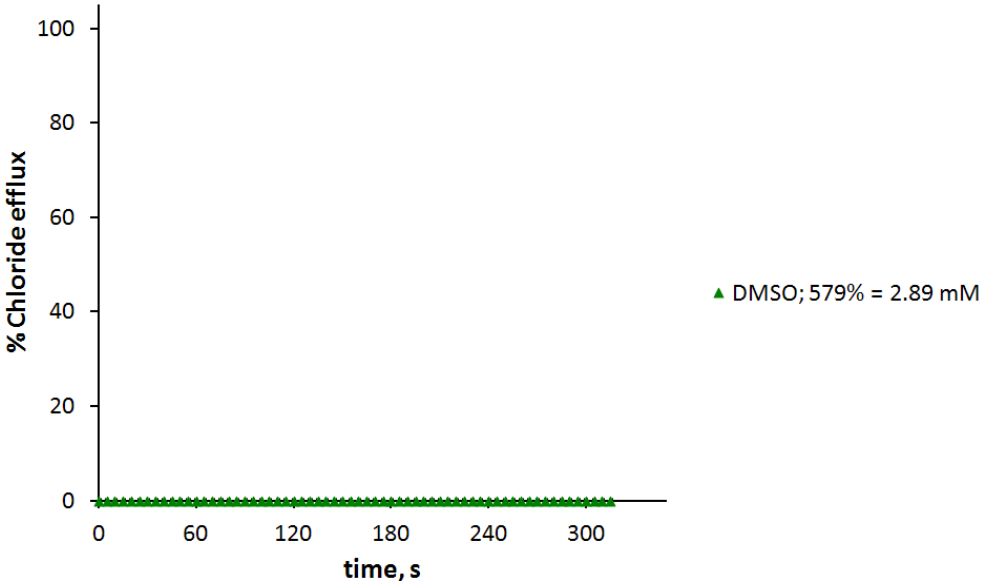

Figure S64: Chloride efflux without the addition of any carrier to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

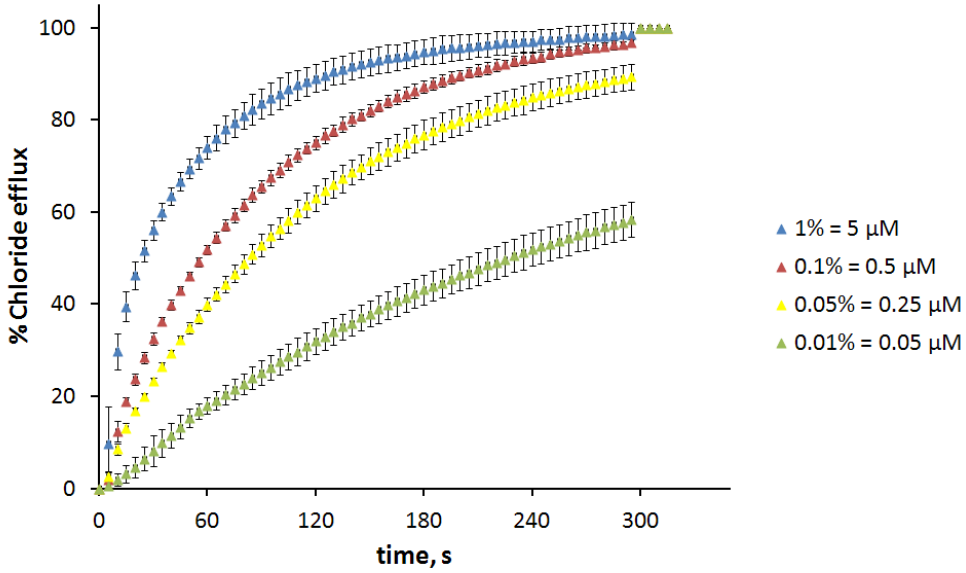

Figure S65: Chloride efflux upon addition of **1** (5 µM, 1 mol%; 0.5 µM, 0.1 mol%; 0.25 µM, 0.05 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

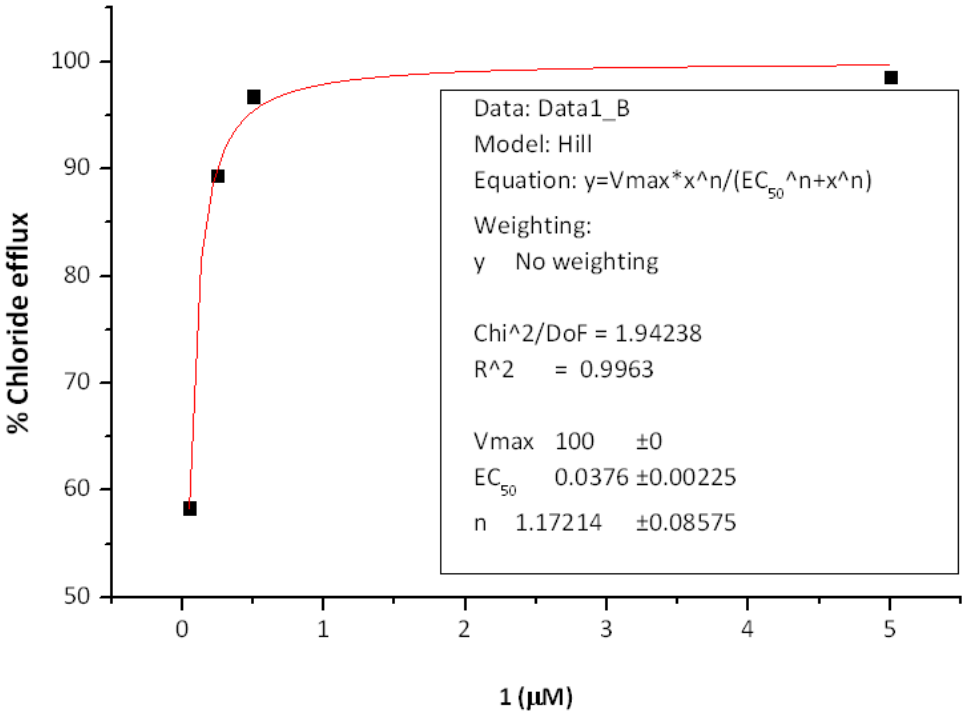

Figure S66: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **1**.

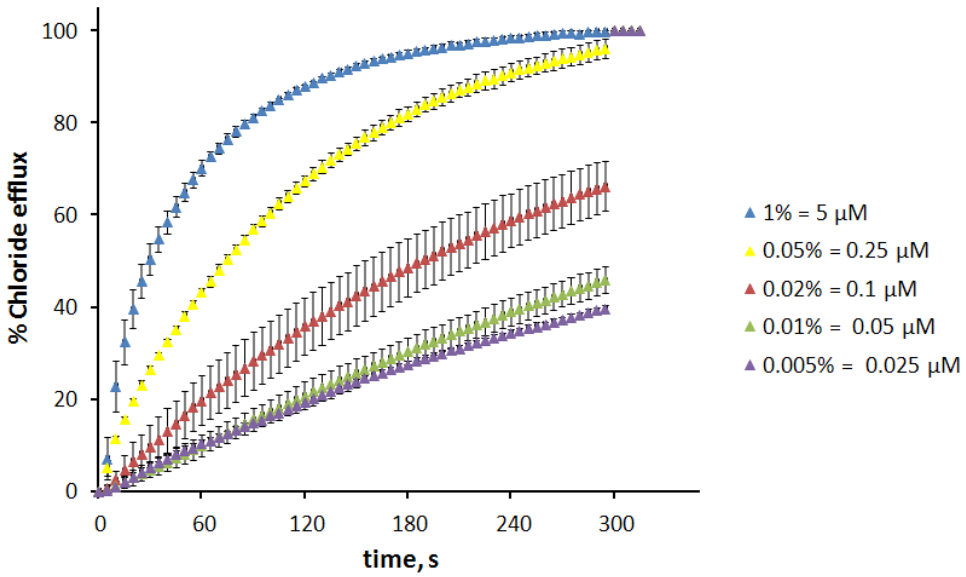

Figure S67: Chloride efflux upon addition of **2** (5 µM, 1 mol%; 0.25 µM, 0,05 mol%; 0.1 µM, 0.02 mol%; 0.05 µM, 0.01 mol% and 0.025 µM, 0.005 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

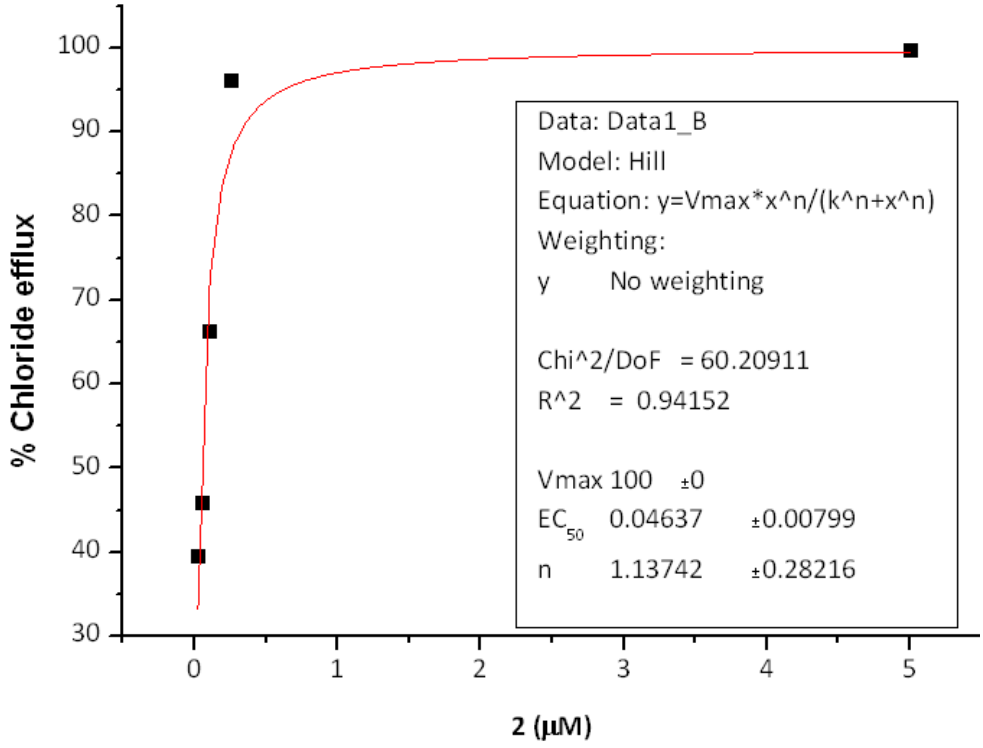

Figure S68: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **2**.

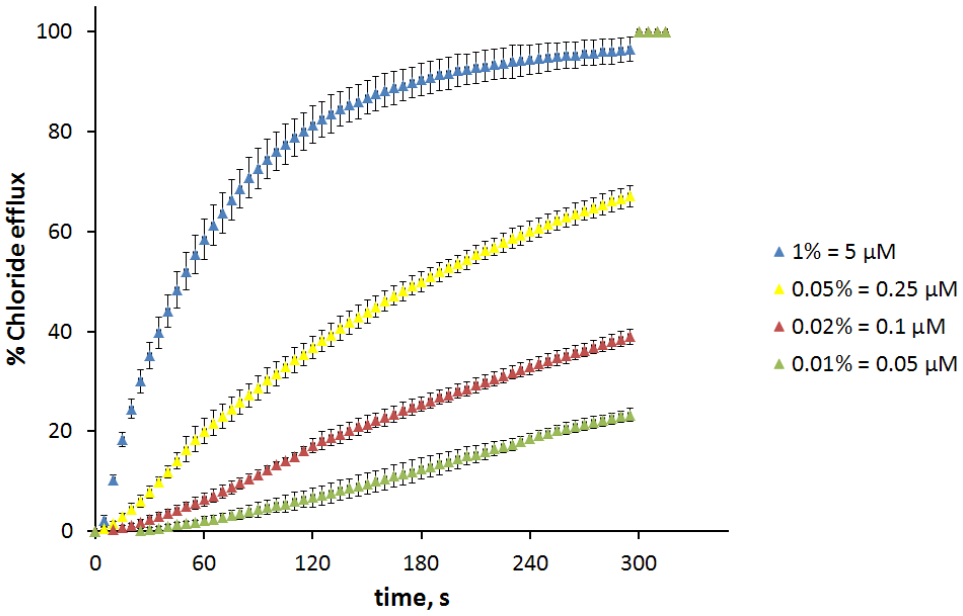

Figure S69: Chloride efflux upon addition of **3** (5 µM, 1 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

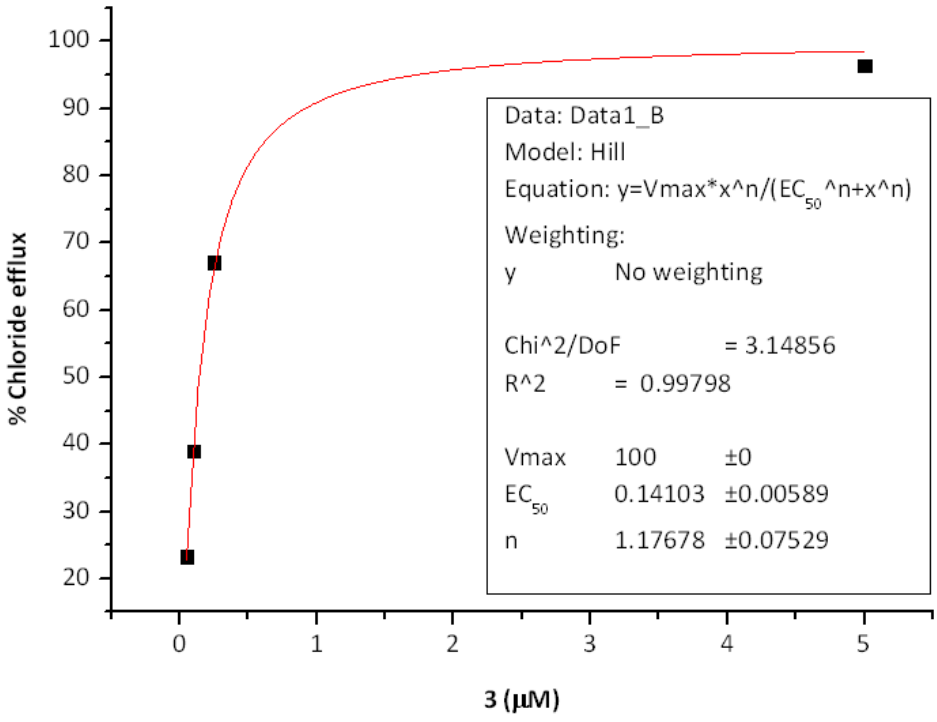

Figure S70: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **3**.

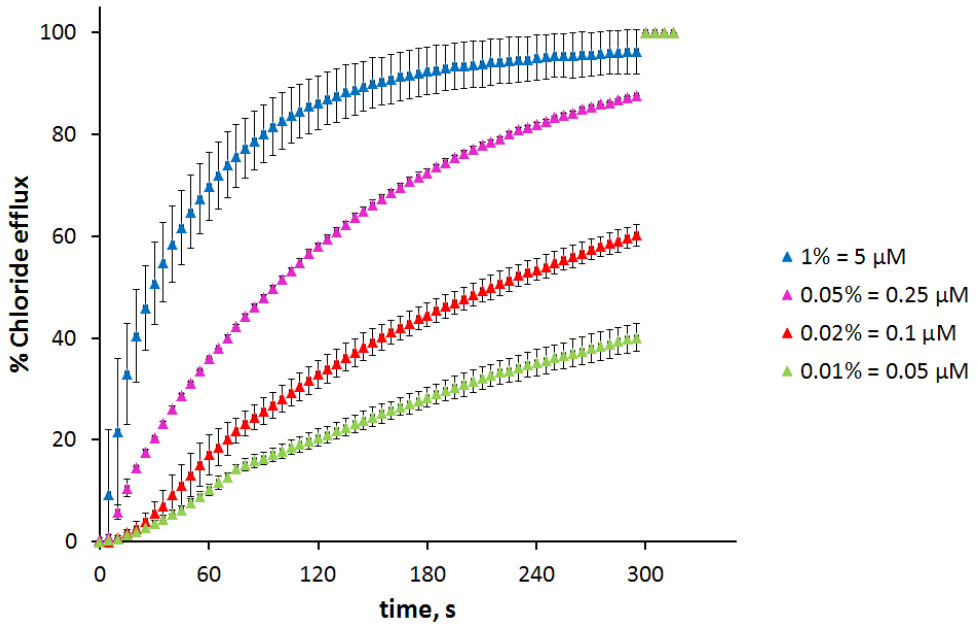

Figure S71: Chloride efflux upon addition of **4** (5 µM, 1 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different independent experiments.

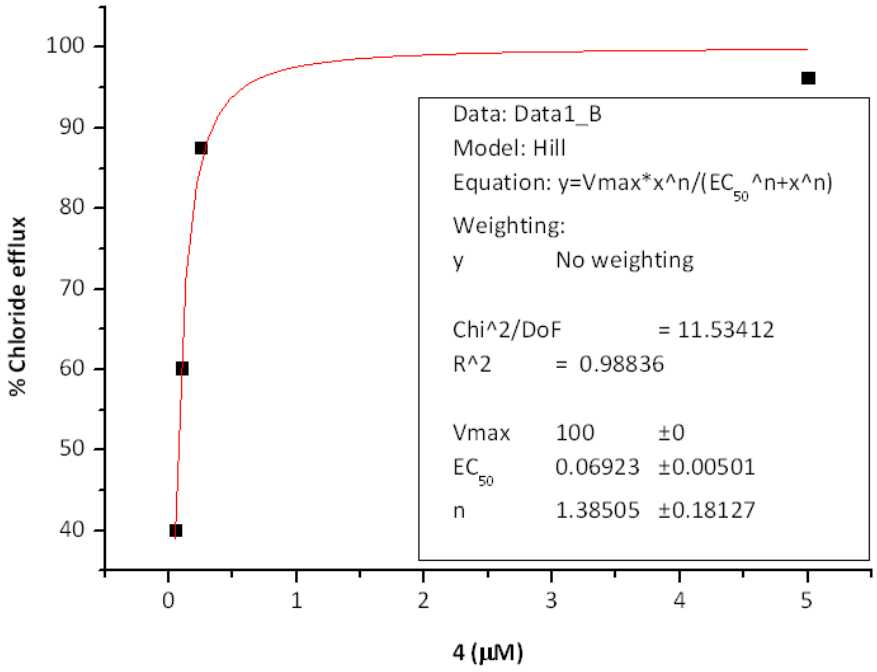

Figure S72: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **4**.

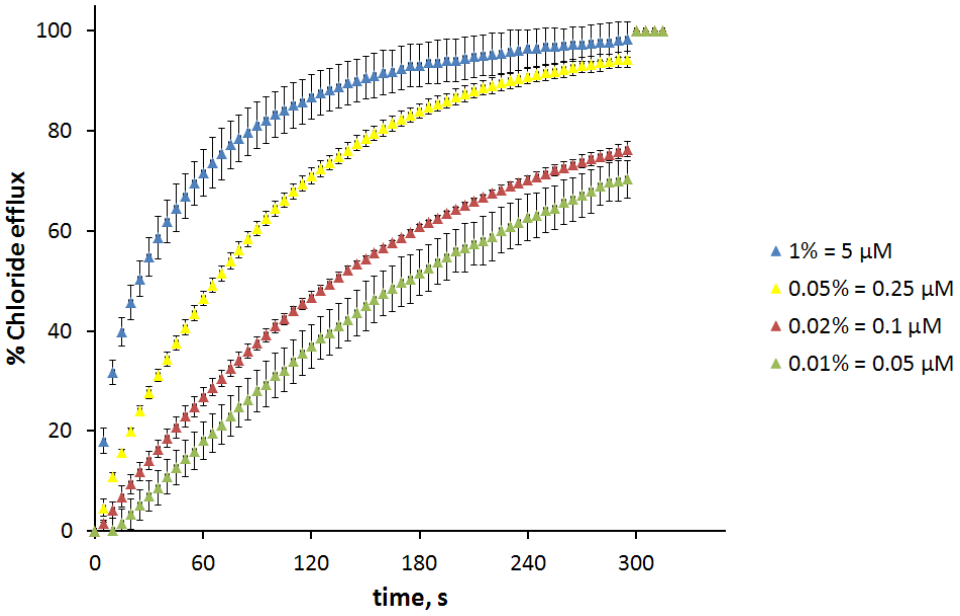

Figure S73: Chloride efflux upon addition of **5** (5 µM, 1 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such.

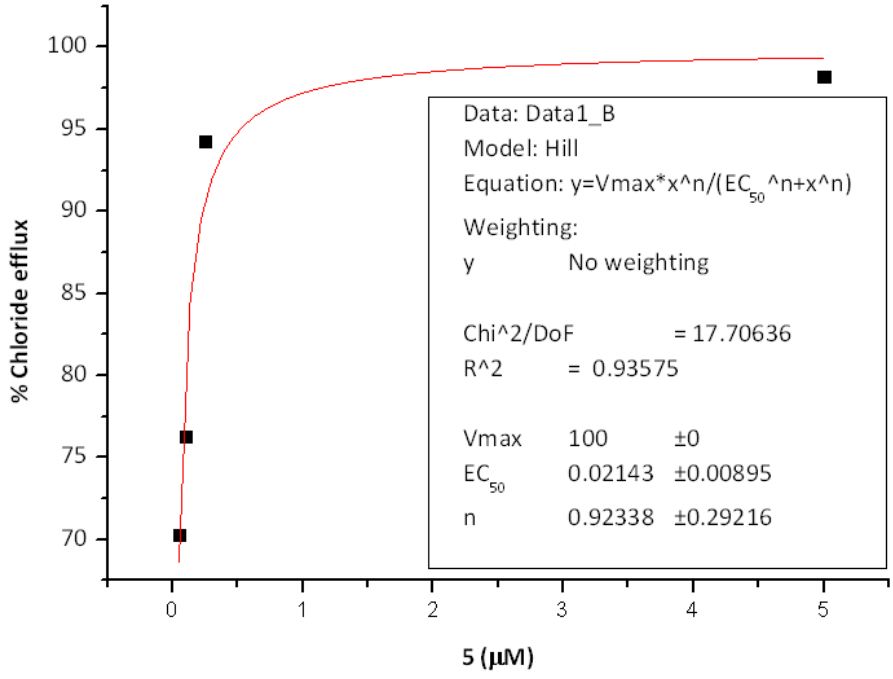

Figure S74: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **5**.

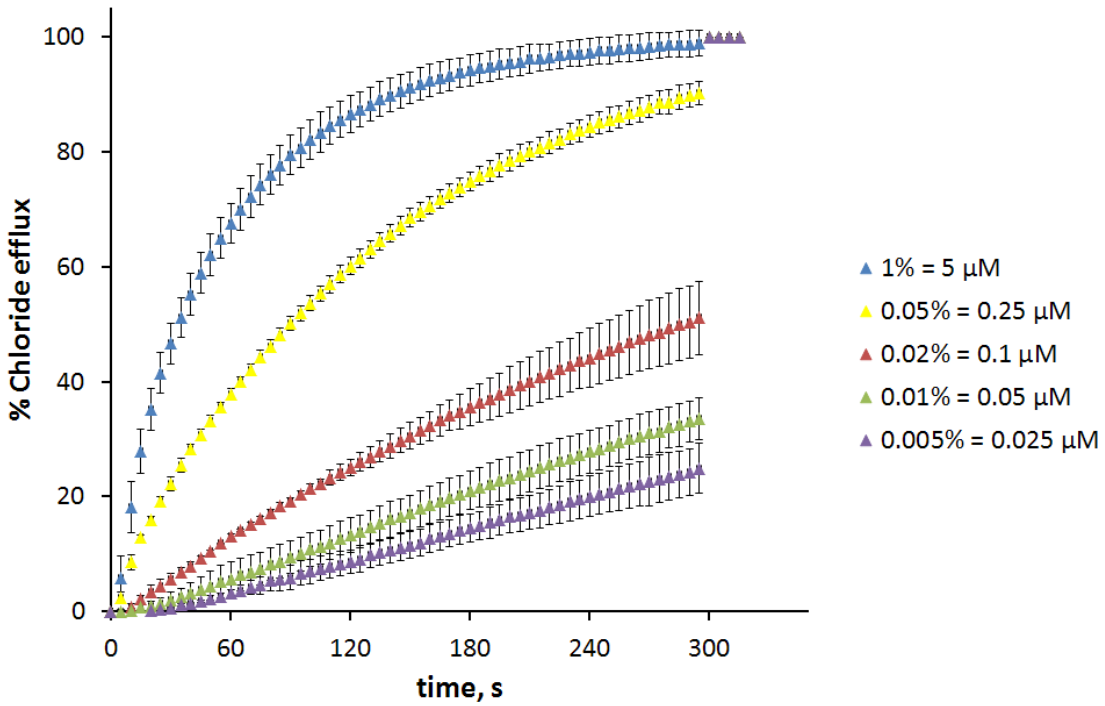

Figure S75: Chloride efflux upon addition of **6** (5 µM, 1 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol%; 0.05 µM, 0.01 mol% and 0.025 µM, 0.005 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

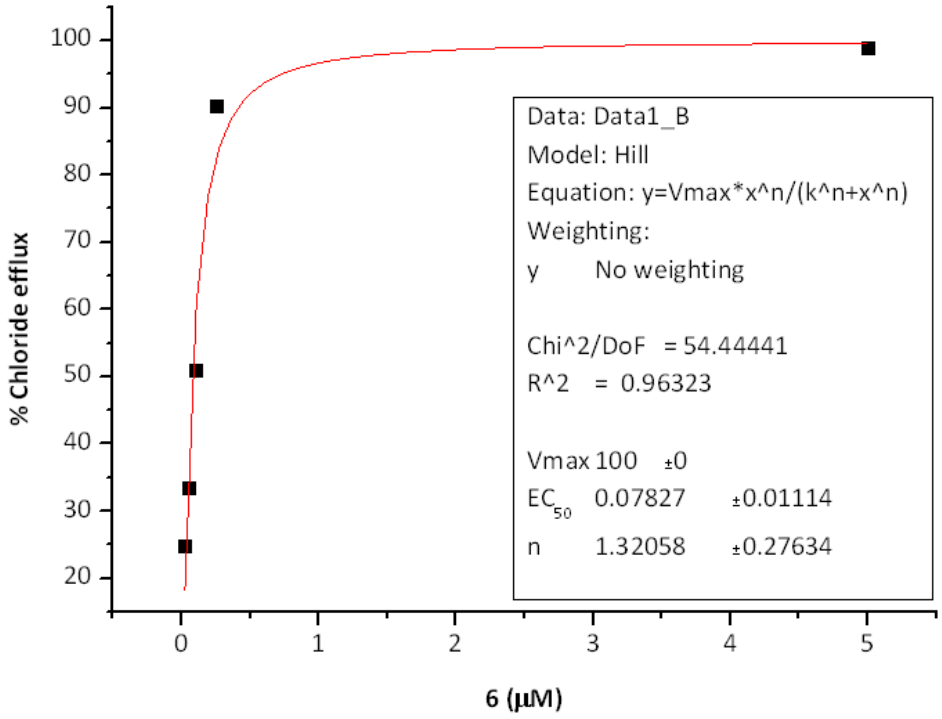

Figure S76: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **6**.

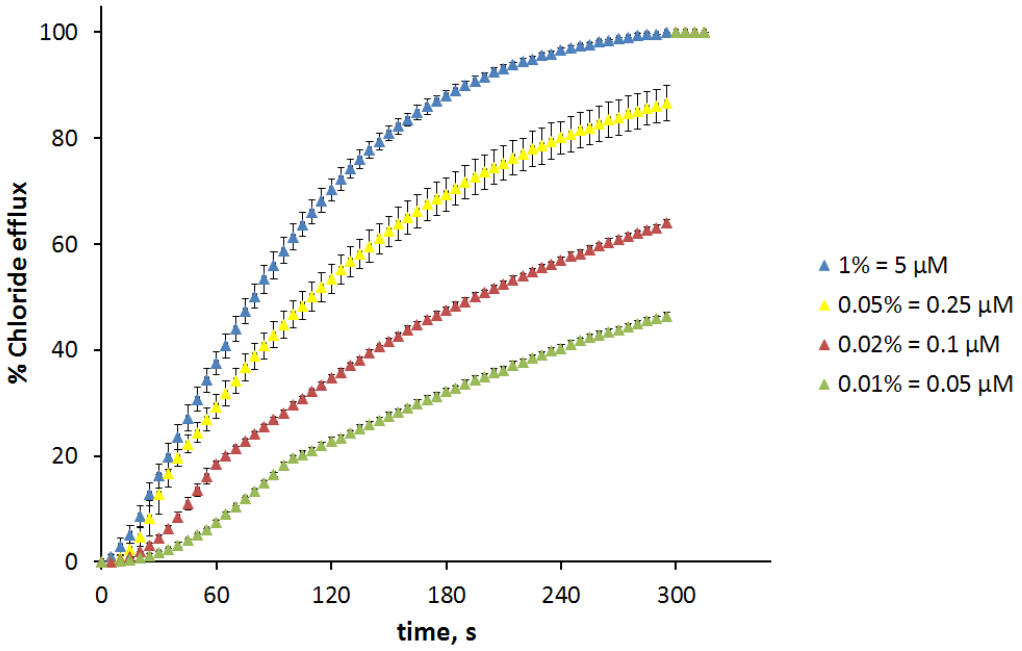

Figure S77: Chloride efflux upon addition of **7** (5 µM, 1 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol%; 0.05 µM, 0.01 mol% and 0.025 µM, 0.005 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

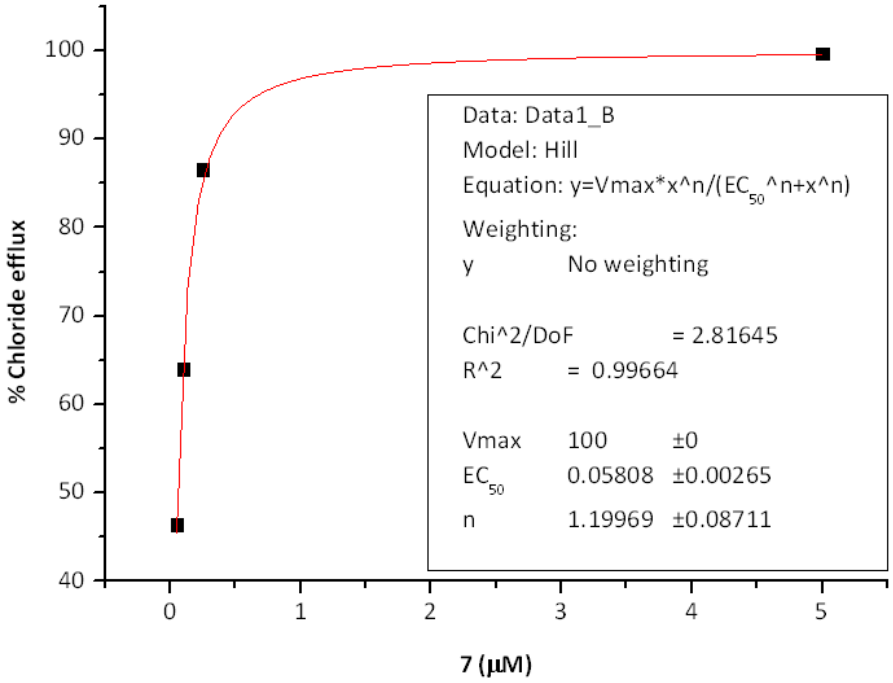

Figure S78: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **7**.

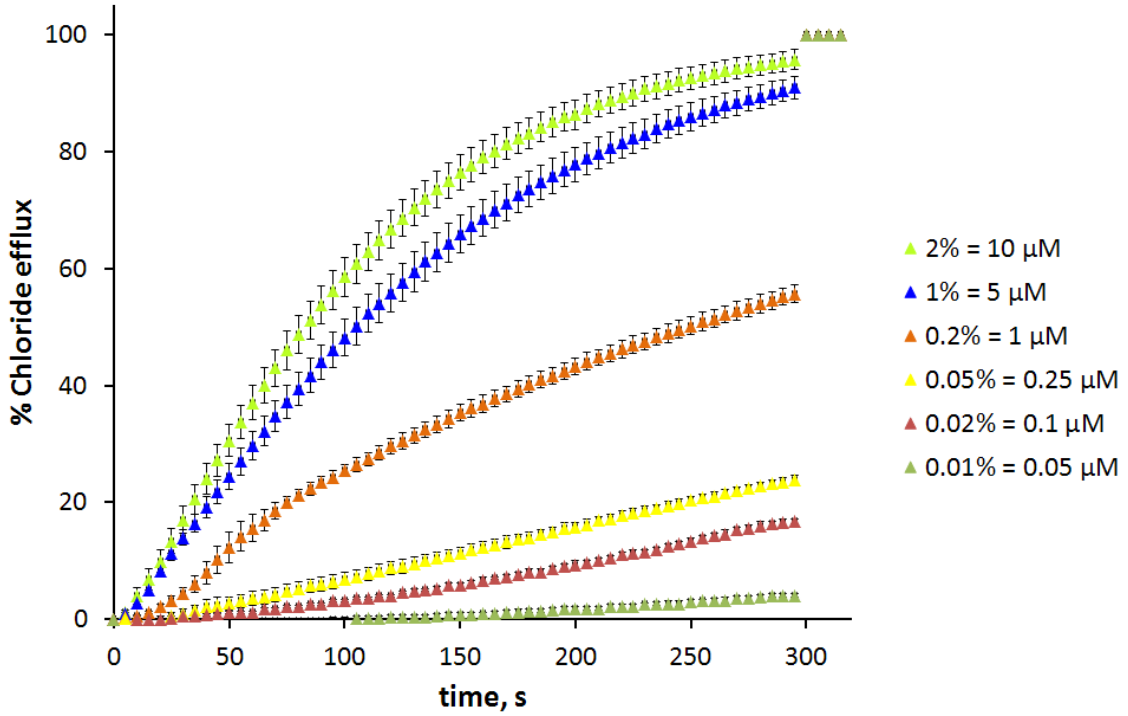

Figure S79: Chloride efflux upon addition of **8** (10 µM, 2 mol%; 5 µM, 1 mol%; 1 µM, 0.2 mol%; 0.25 µM, 0.05 mol%; 0.1 µM, 0.02 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

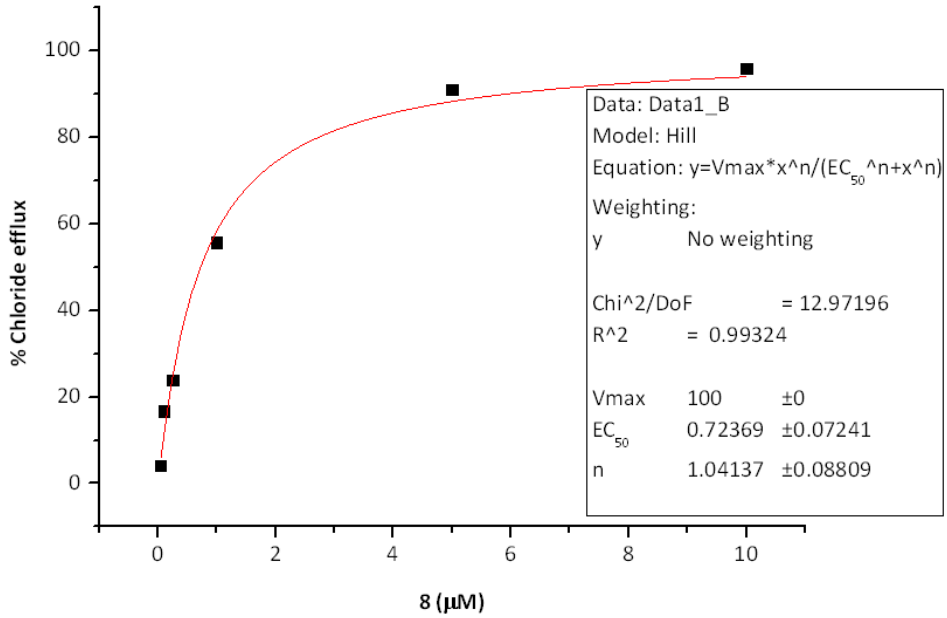

Figure S80: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **8**.

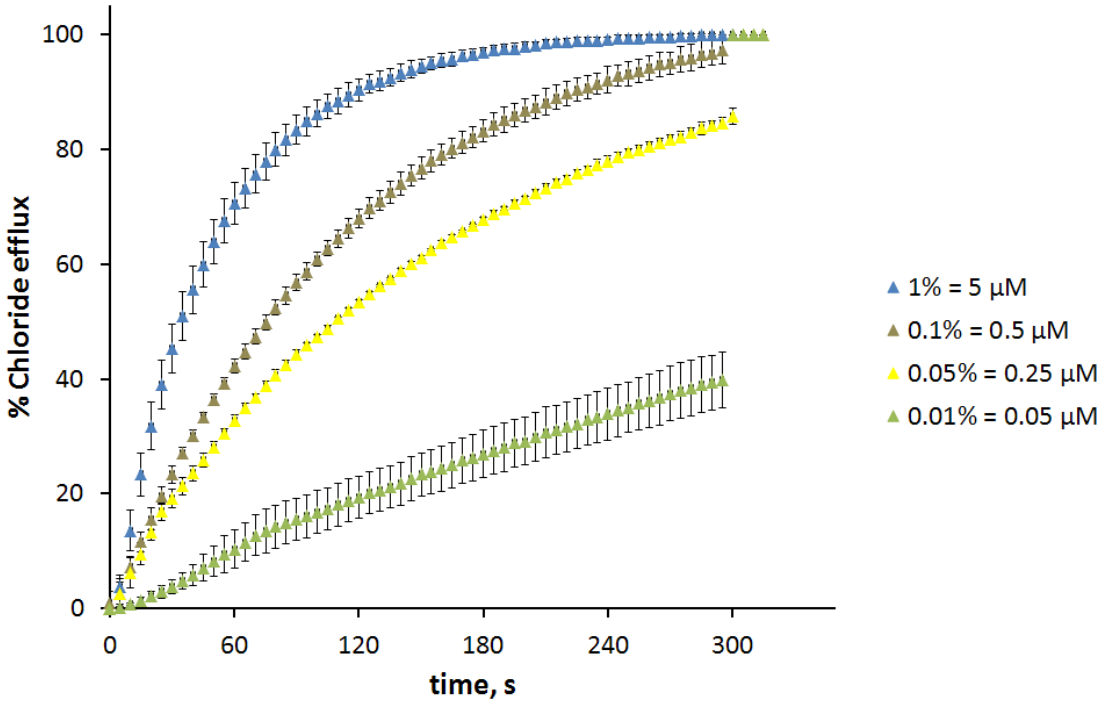

Figure S81: Chloride efflux upon addition of **9** (5 µM, 1 mol%; 0.5 µM, 0.1 mol%; 0.25 µM, 0.05 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

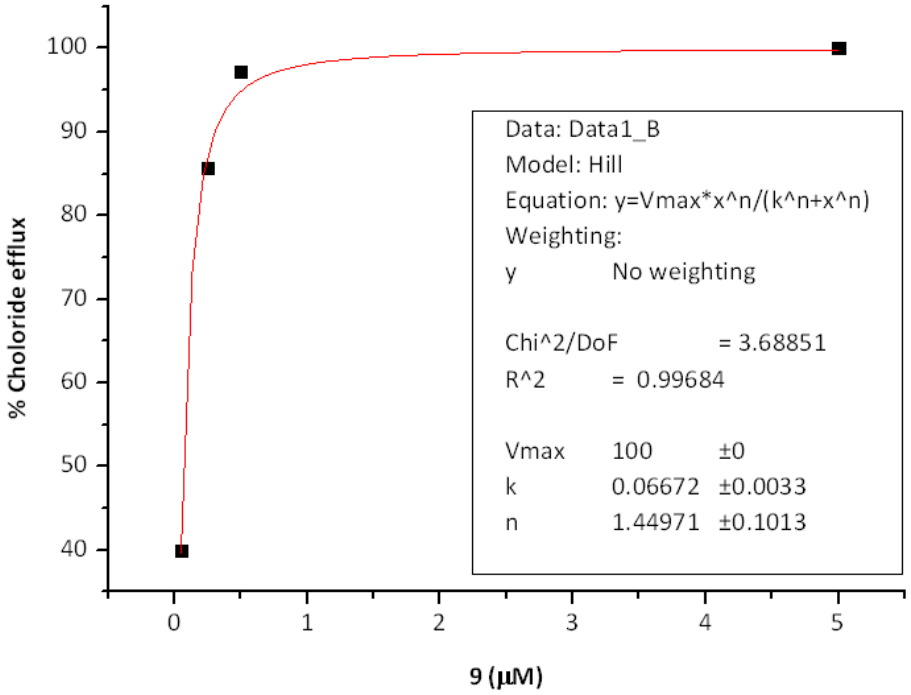

Figure S82: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **9**.

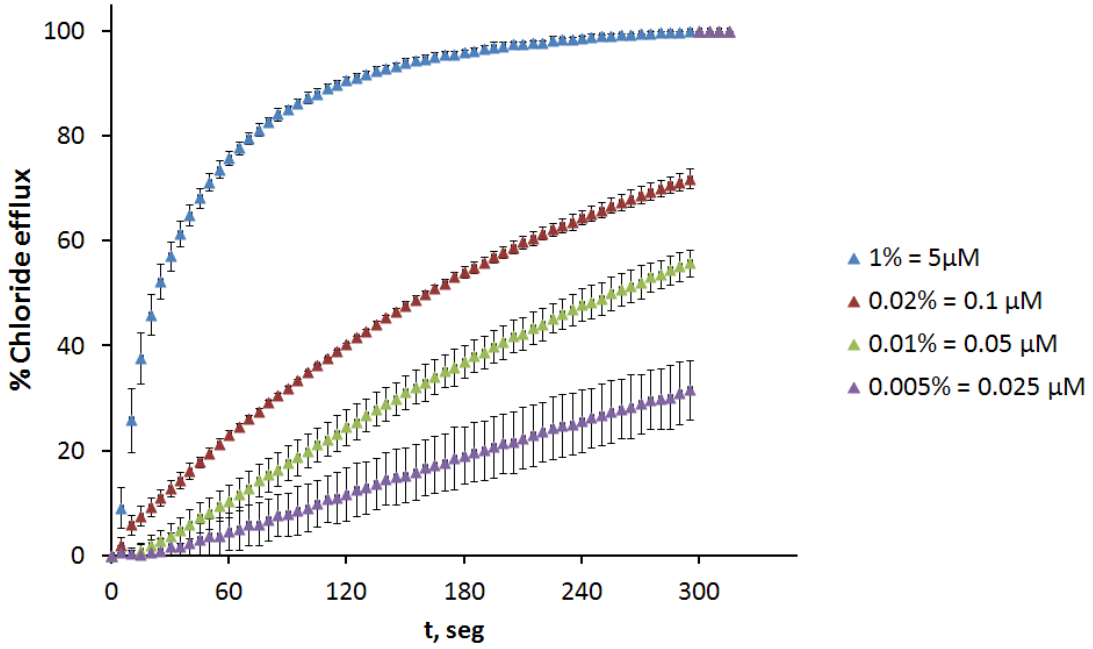

Figure S83: Chloride efflux upon addition of **10** (5 µM, 1 mol%; 0.1 µM, 0.02 mol%; 0.05 µM, 0.01 mol% and 0.025 µM, 0.005 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

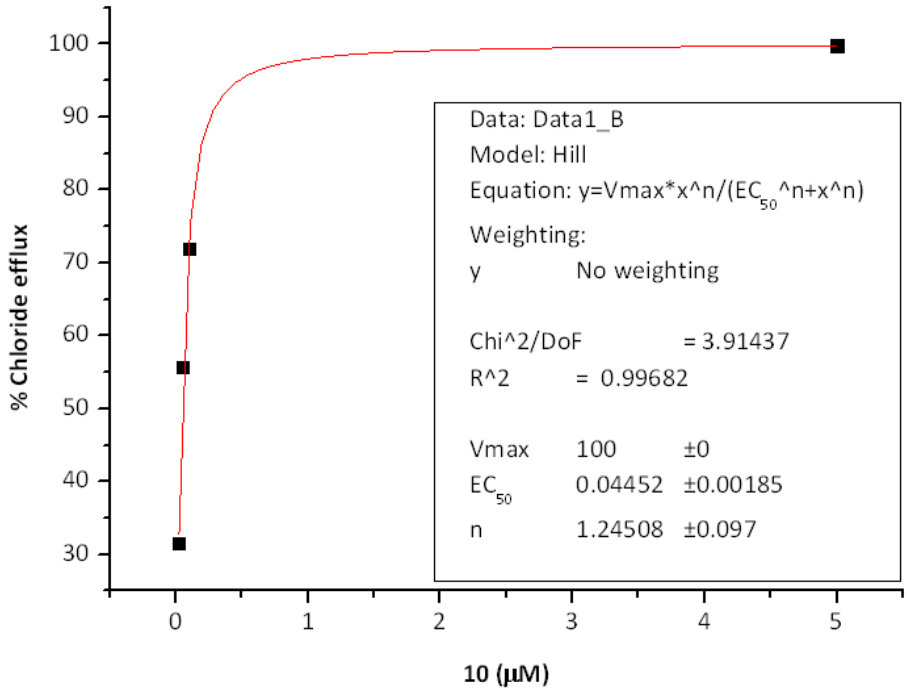

Figure S84: Hill analysis for Cl^-/NO_3^- antiport mediated by compound **10**.

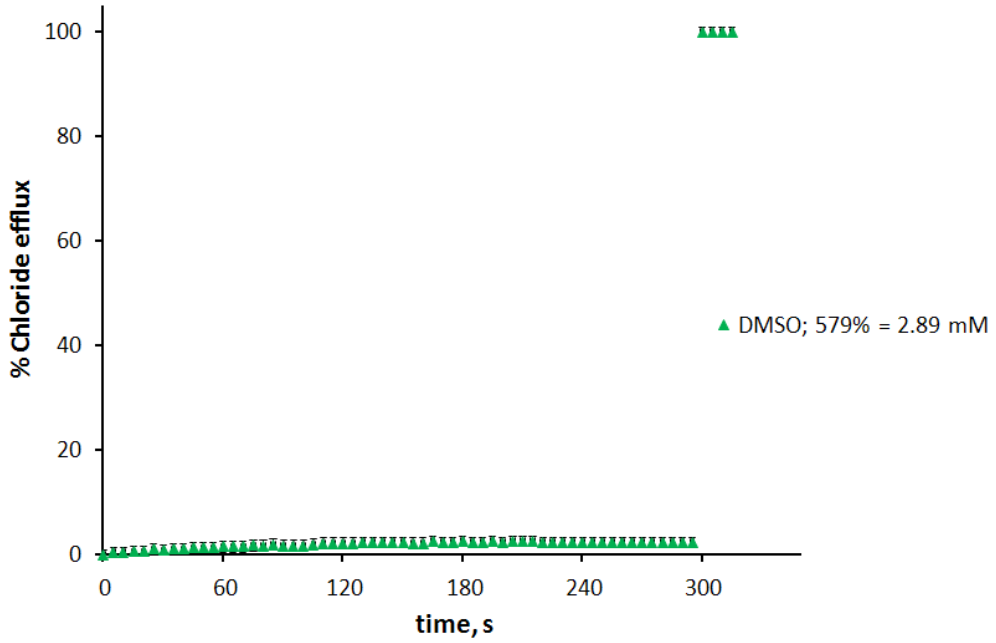

Figure S85: Chloride efflux without the addition of any carrier to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) and were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such.

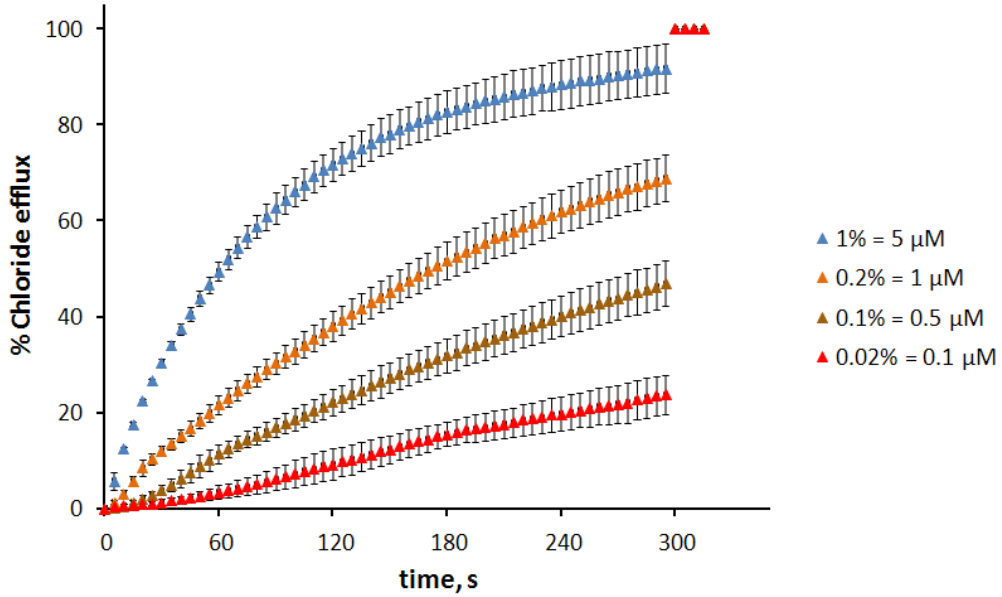

Figure S86: Chloride efflux upon addition of **1** (5 µM, 1 mol%; 1 µM, 0.2 mol%; 0.5 µM, 0.1 mol% and 0.1 µM, 0.02 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

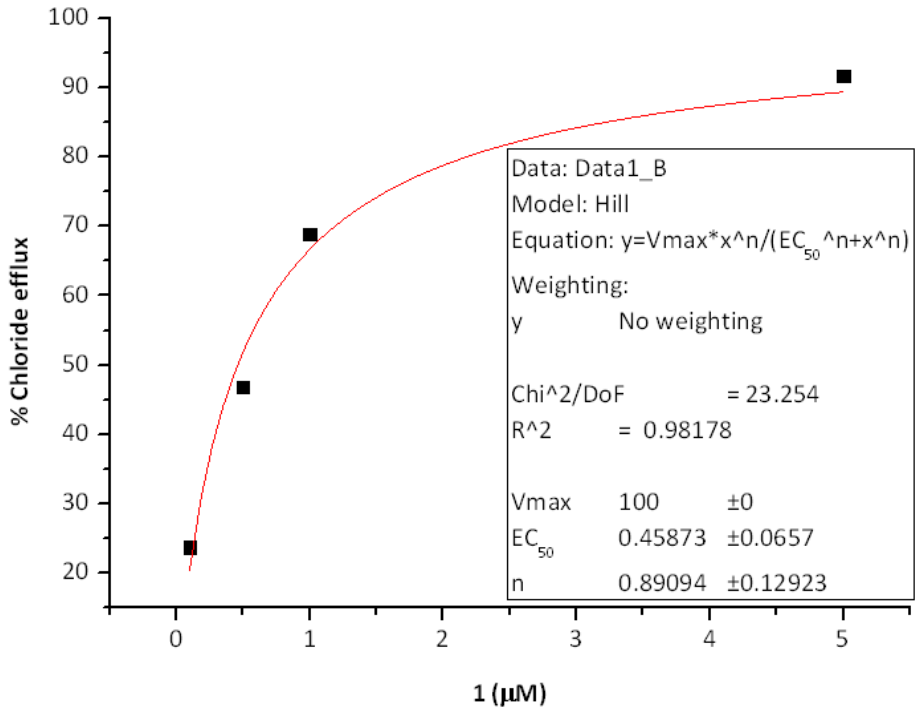

Figure S87: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **1**.

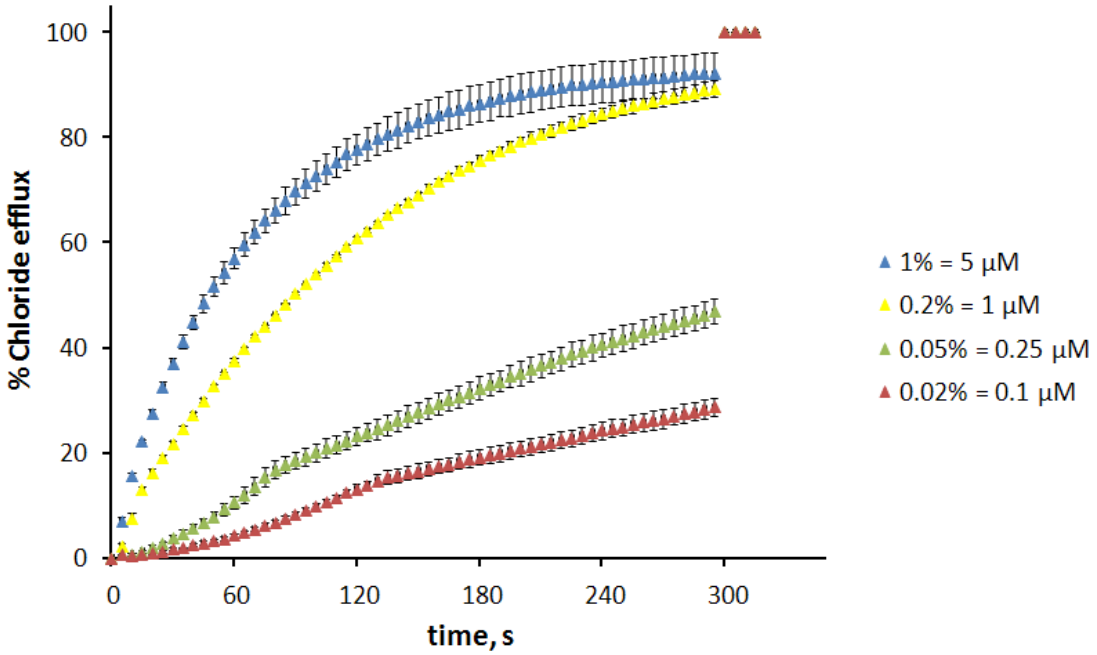

Figure S88: Chloride efflux upon addition of **2** (5 μM, 1 mol%; 1 μM, 0.2 mol%; 0.25 μM, 0.05 mol% and 0.1 μM, 0.02 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

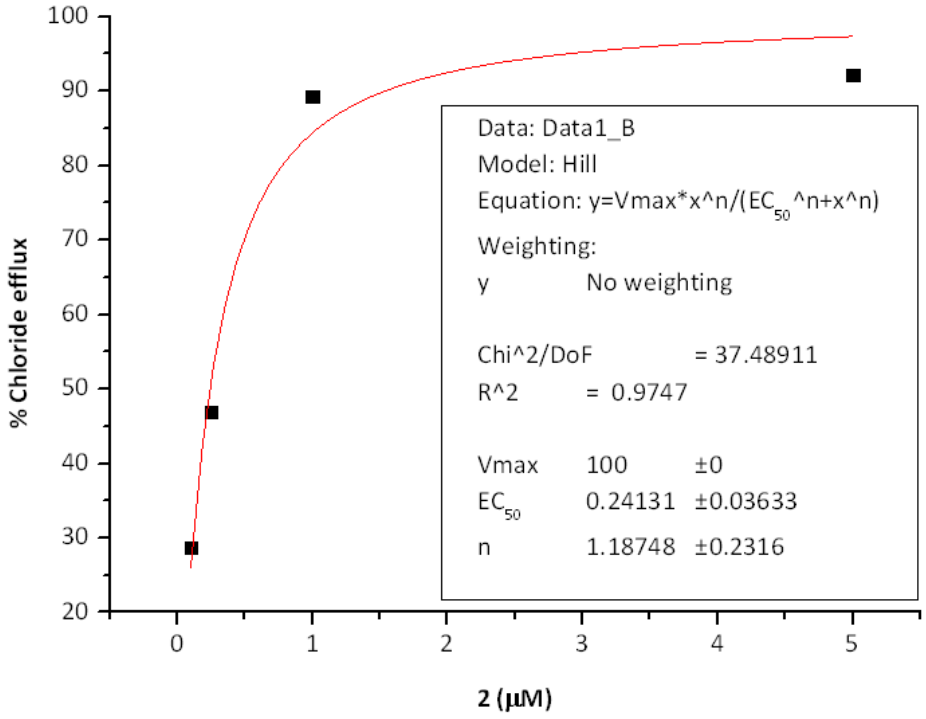

Figure S89: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **2**.

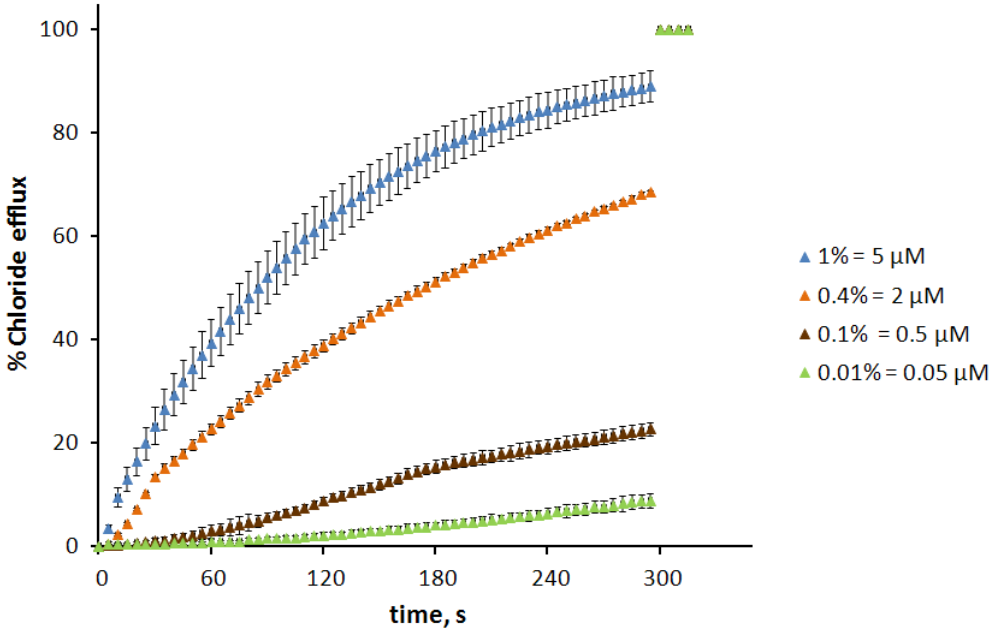

Figure S90: Chloride efflux upon addition of **3** (5 μM, 1 mol%; 2 μM, 0.4 mol%; 0.5 μM, 0.1 mol% and 0.05 μM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

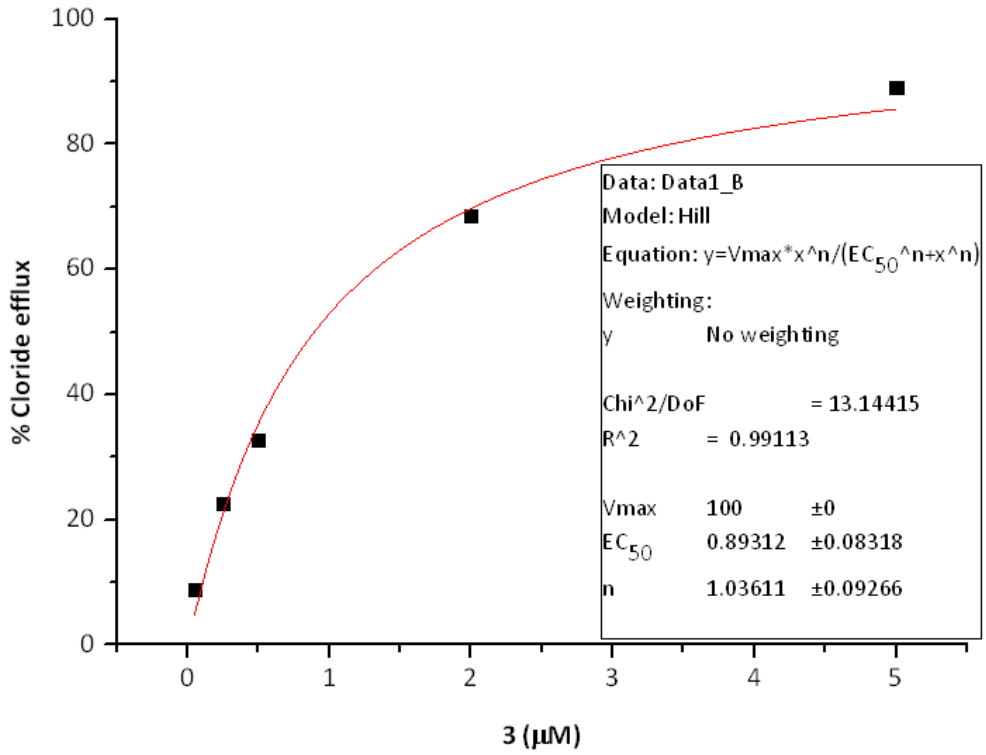

Figure S91: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **3**.

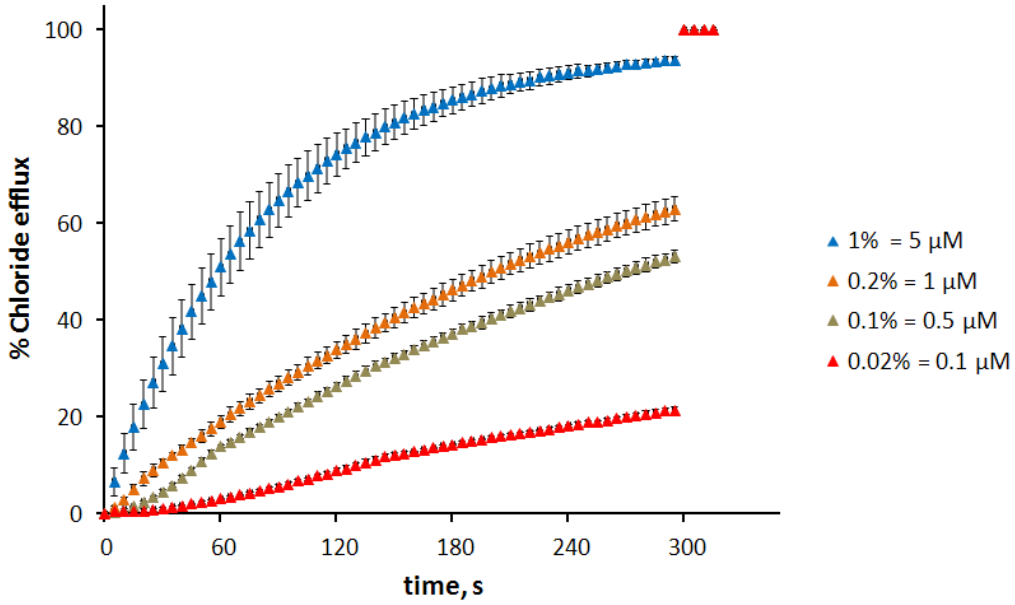

Figure S92: Chloride efflux upon addition of **4** (5 µM, 1 mol%; 1 µM, 0.2 mol%; 0.5 µM, 0.1 mol% and 0.1 µM, 0.02 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

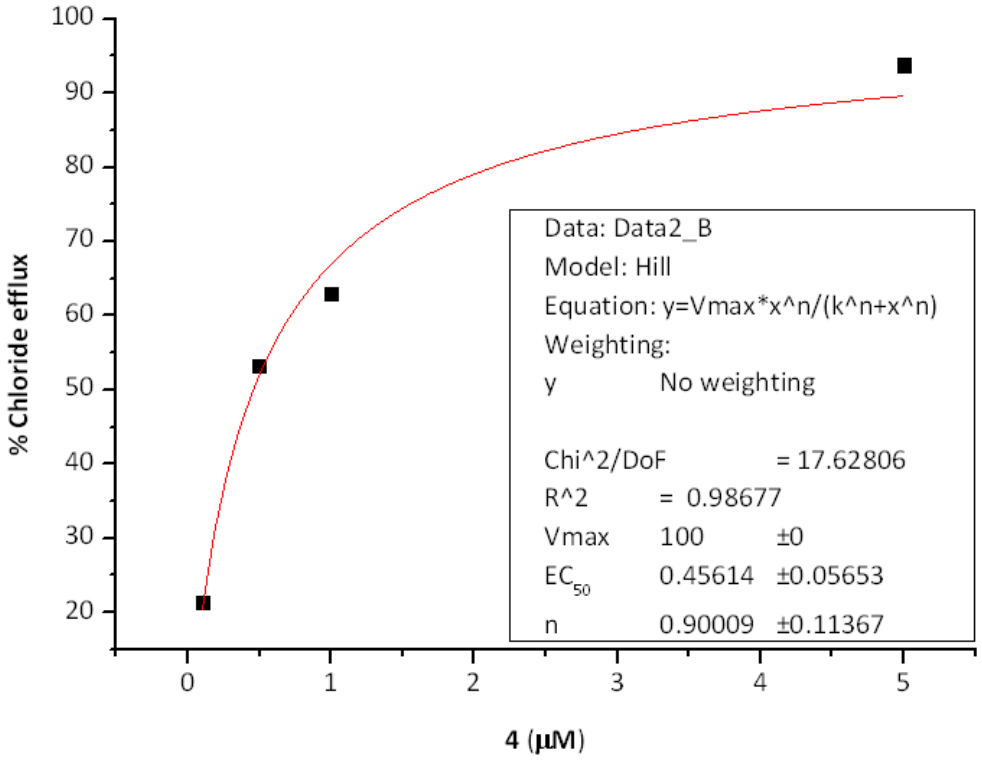

Figure S93: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **4**.

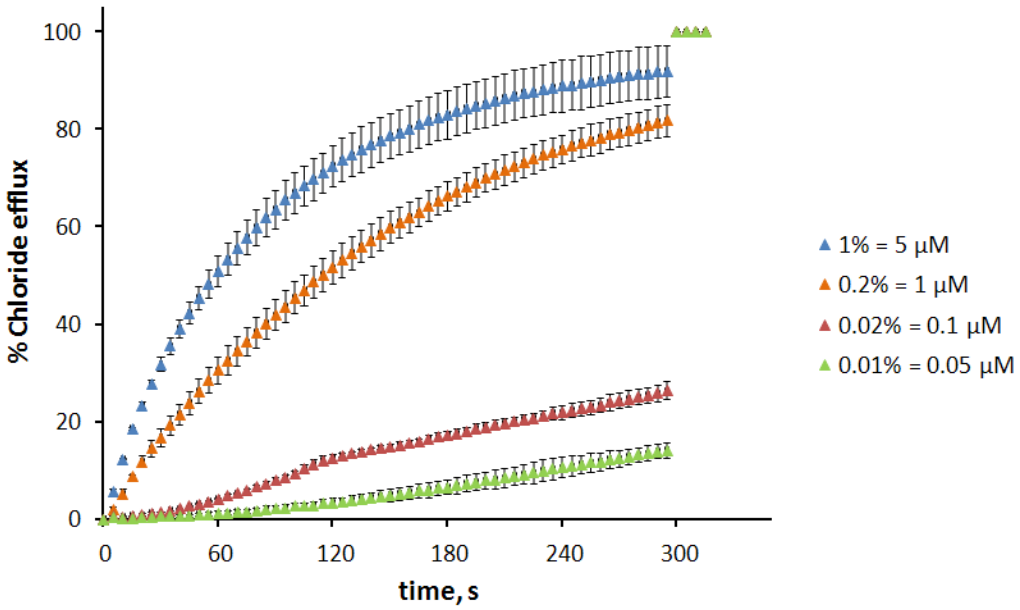

Figure S94: Chloride efflux upon addition of **5** (5 µM, 1 mol%; 1 µM, 0.2 mol%; 0.1 µM, 0.02 mol% and 0.05 µM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

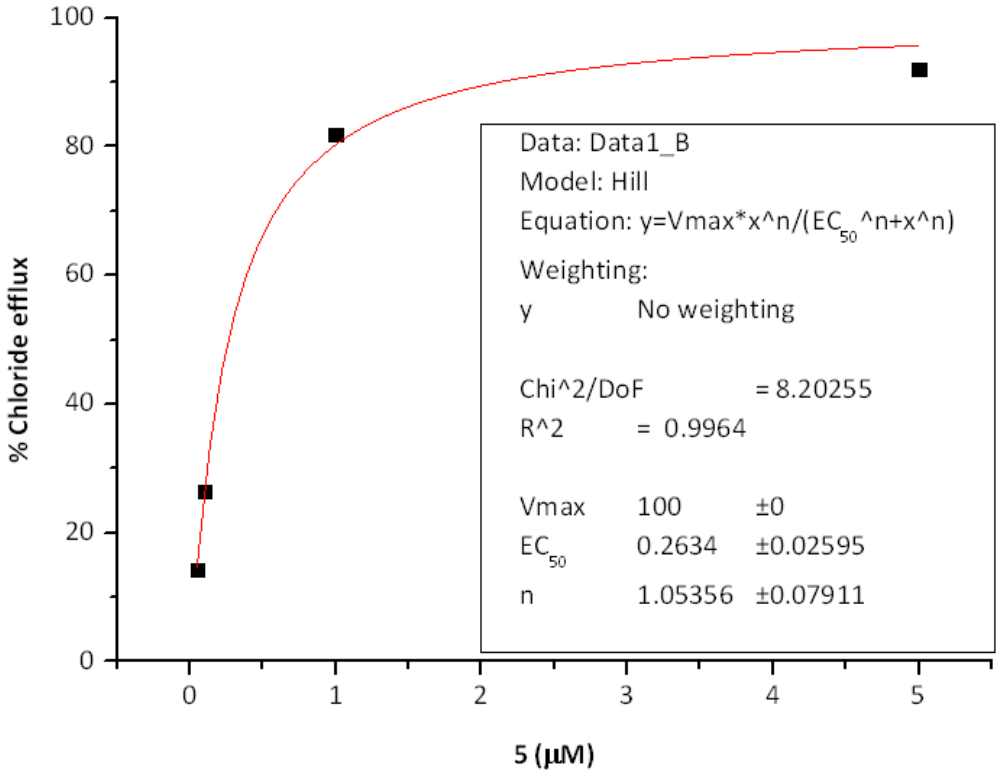

Figure S95: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **5**.

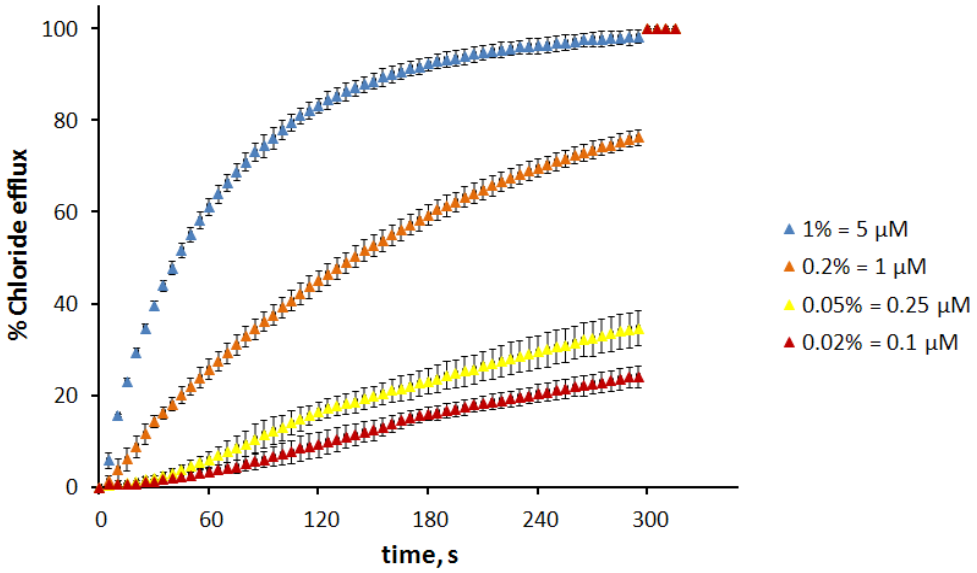

Figure S96: Chloride efflux upon addition of **6** (5 μM, 1 mol%; 1 μM, 0.2 mol%; 0.25 μM, 0.05 mol% and 0.1 μM, 0.02 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

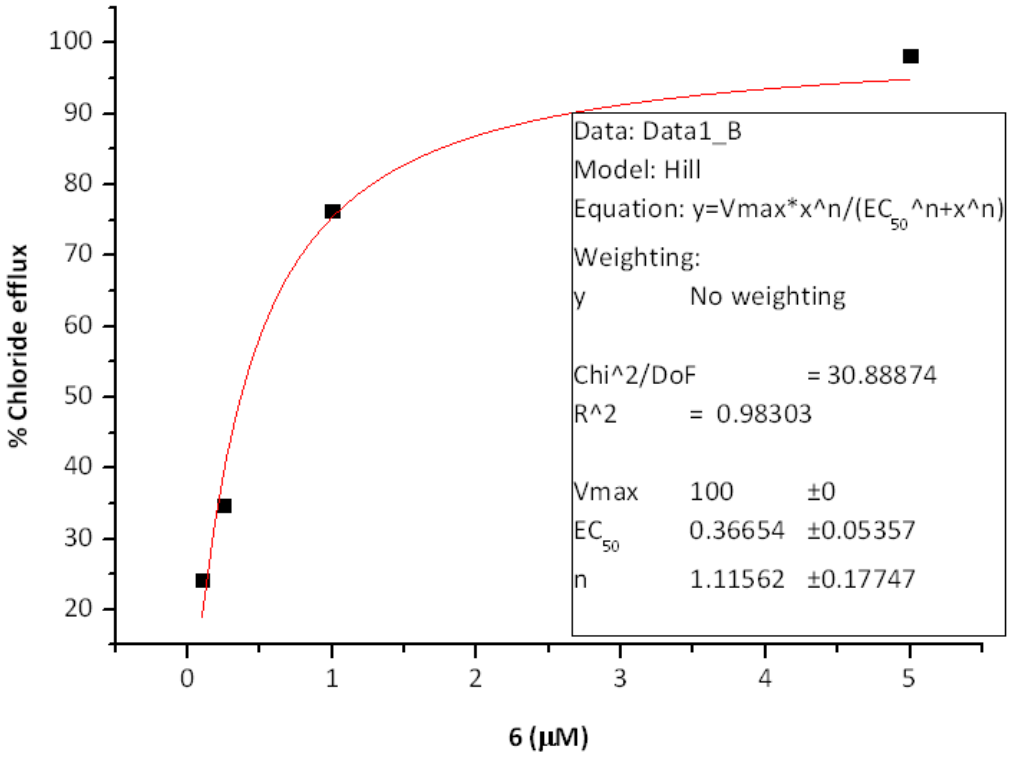

Figure S97: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **6**.

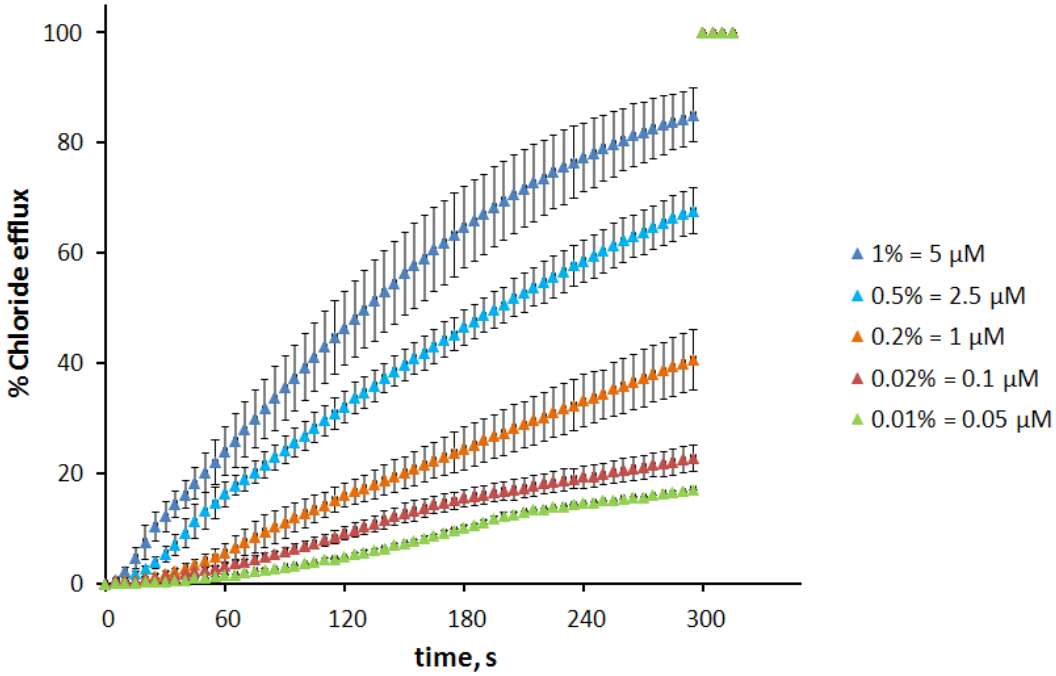

Figure S98: Chloride efflux upon addition of **7** (5 μM, 1 mol%; 2.5 μM, 0.5 mol%; 1 μM, 0.2 mol%; 0.1 μM, 0.02 mol% and 0.05 μM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

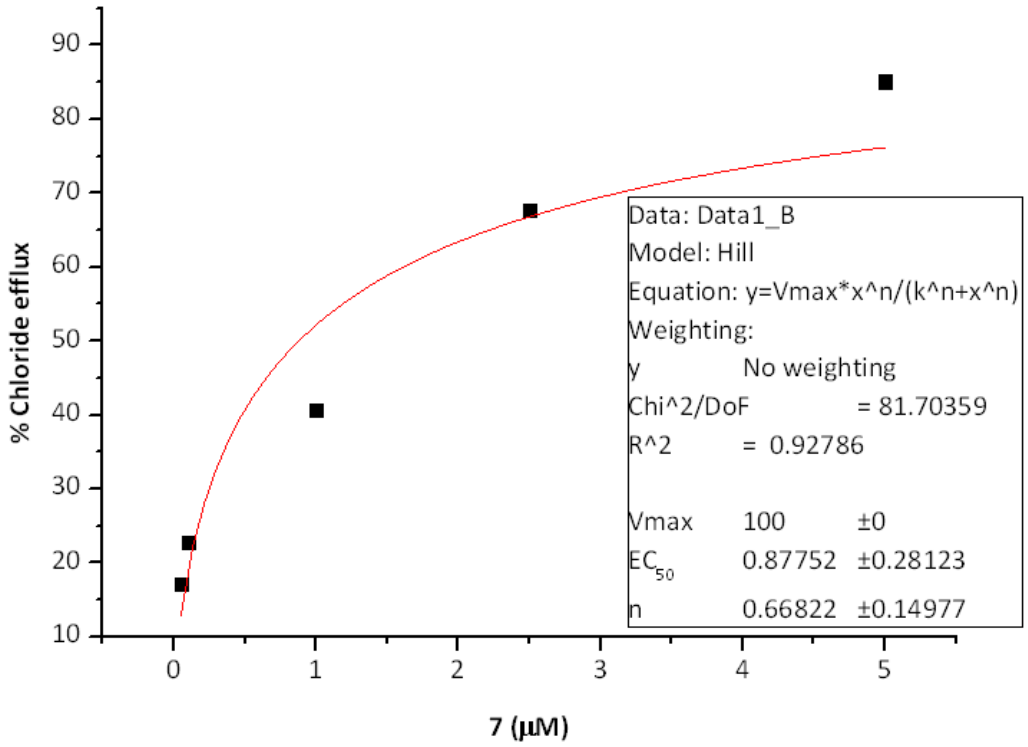

Figure S99: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **7**.

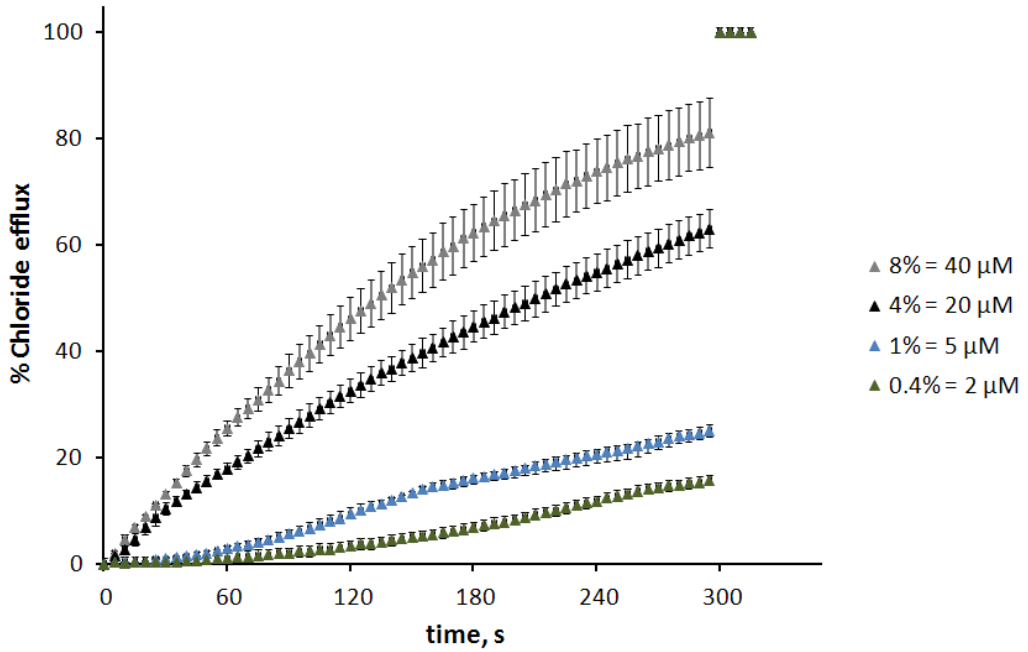

Figure S100: Chloride efflux upon addition of **8** (40 µM, 8 mol%; 20 µM, 4 mol%; 5 µM, 1 mol% and 2 µM, 0.4 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

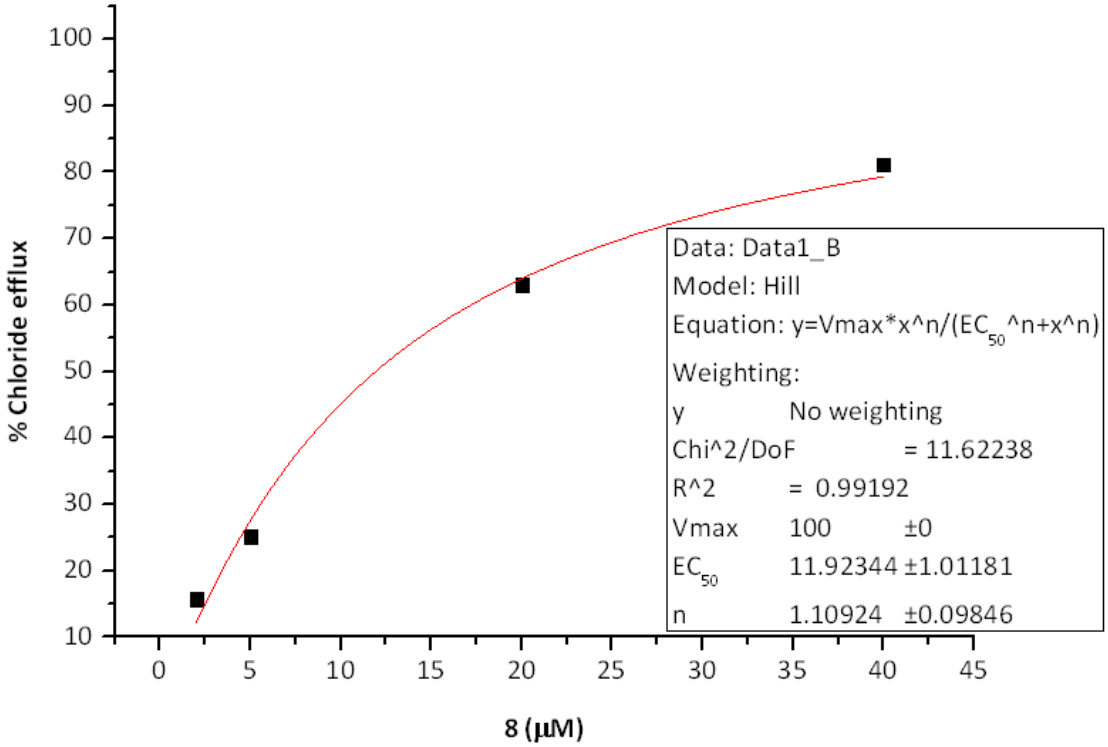

Figure S101: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **8**.

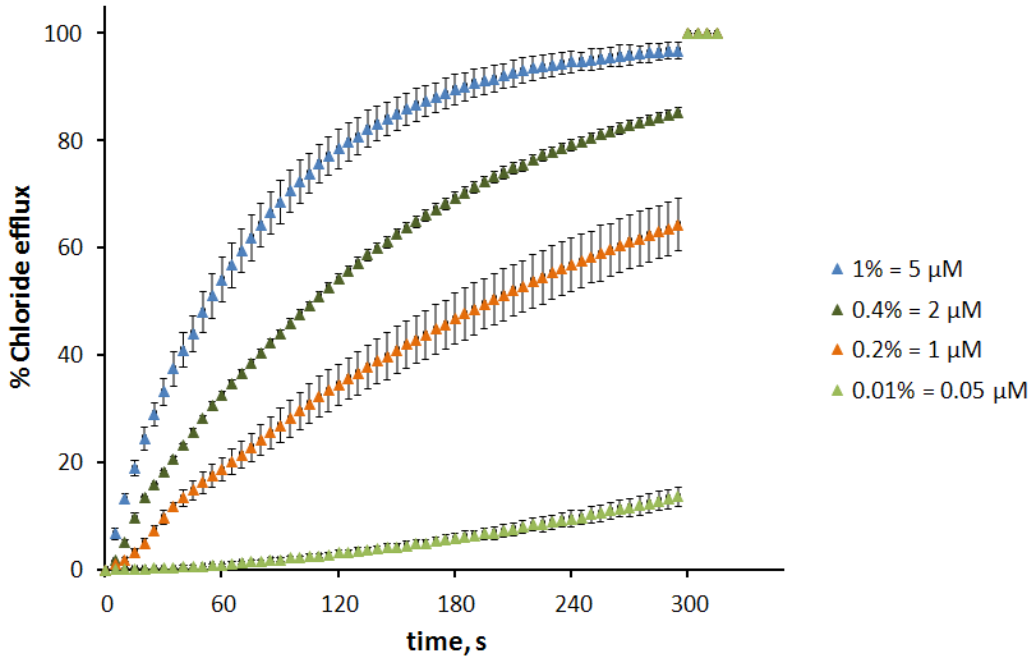

Figure S102: Chloride efflux upon addition of **9** (5 μM, 1 mol%; 2 μM, 0.4 mol%; 1 μM, 0.2 mol% and 0.05 μM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

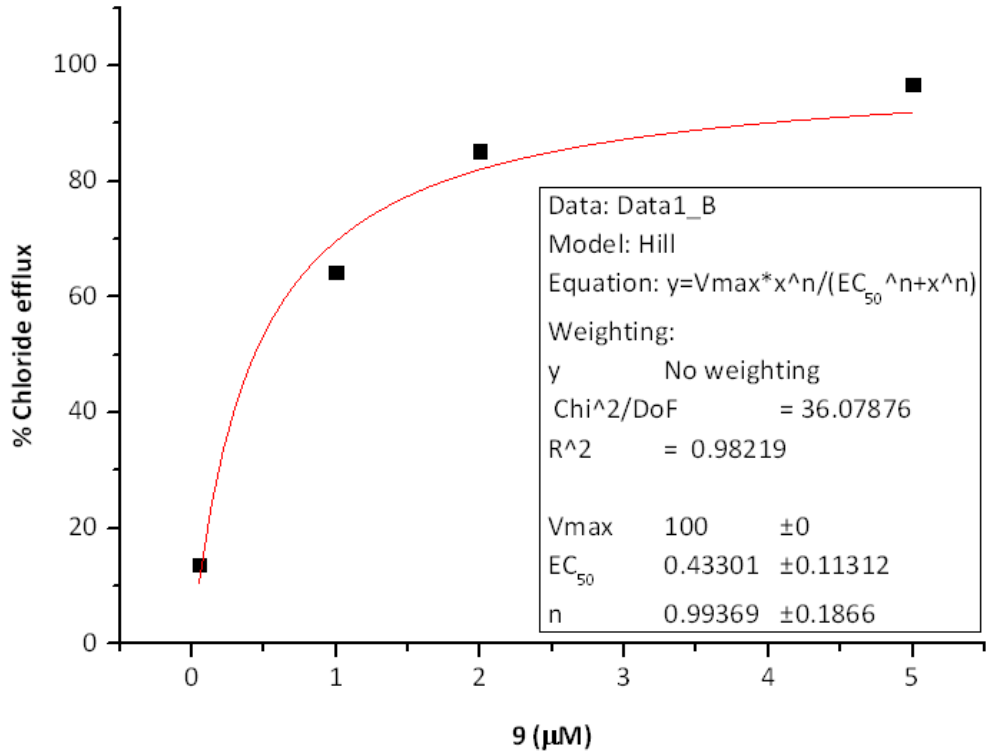

Figure S103: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **9**.

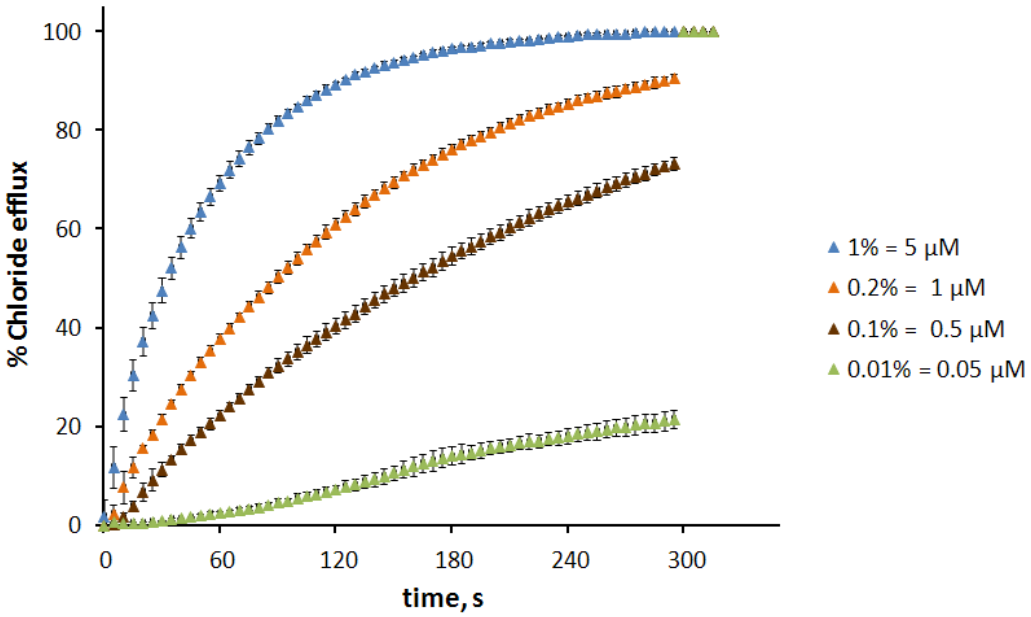

Figure S104: Chloride efflux upon addition of **10** (5 μM, 1 mol%; 1 μM, 0.2 mol%; 0.5 μM, 0.1 mol% and 0.05 μM, 0.01 mol% carrier to lipid) to vesicles composed of POPC. The vesicles contained NaCl (451 mM NaCl and 20 mM phosphate buffer, pH 7.2) were immersed in Na_2SO_4 (150 mM Na_2SO_4; 40 mM HCO_3^- and 20 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

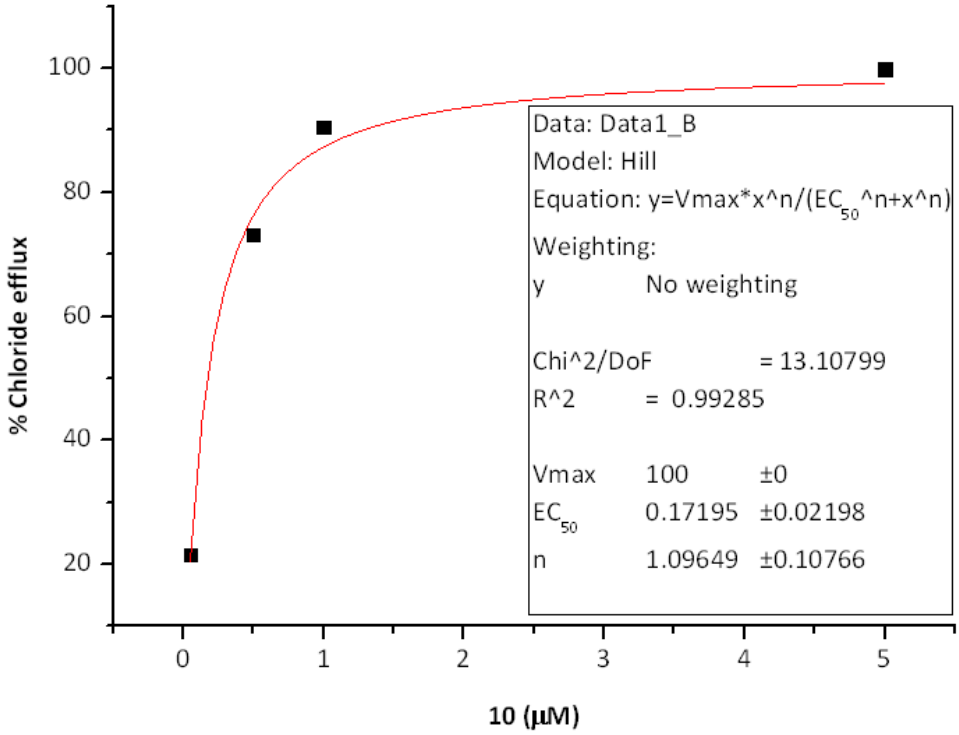

Figure S105: Hill analysis for Cl^-/HCO_3^- antiport mediated by compound **10**.

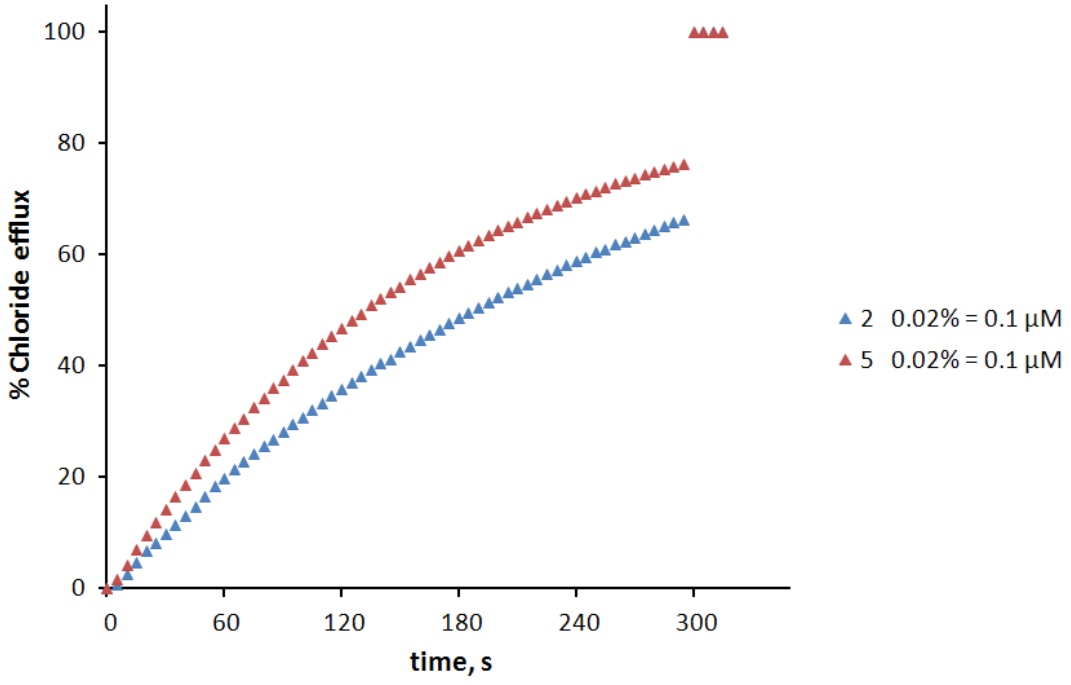

Figure S106: Comparative chloride efflux induced by compound **2** (0.1 µM, 0.02 mol% carrier to lipid) and **5** (0.1 µM, 0.02 mol% carrier to lipid) from POPC vesicles. The vesicles contained NaCl (488 mM NaCl and 5 mM phosphate buffer, pH 7.2) were immersed in $NaNO_3$ (488 mM $NaNO_3$ and 5 mM phosphate buffer, pH 7.2). At the end of the experiment the vesicles were lysed with detergent to release all chloride ions and the resulting value was considered to represent 100% release and used as such. Each trace represents an average of at least three different experiments.

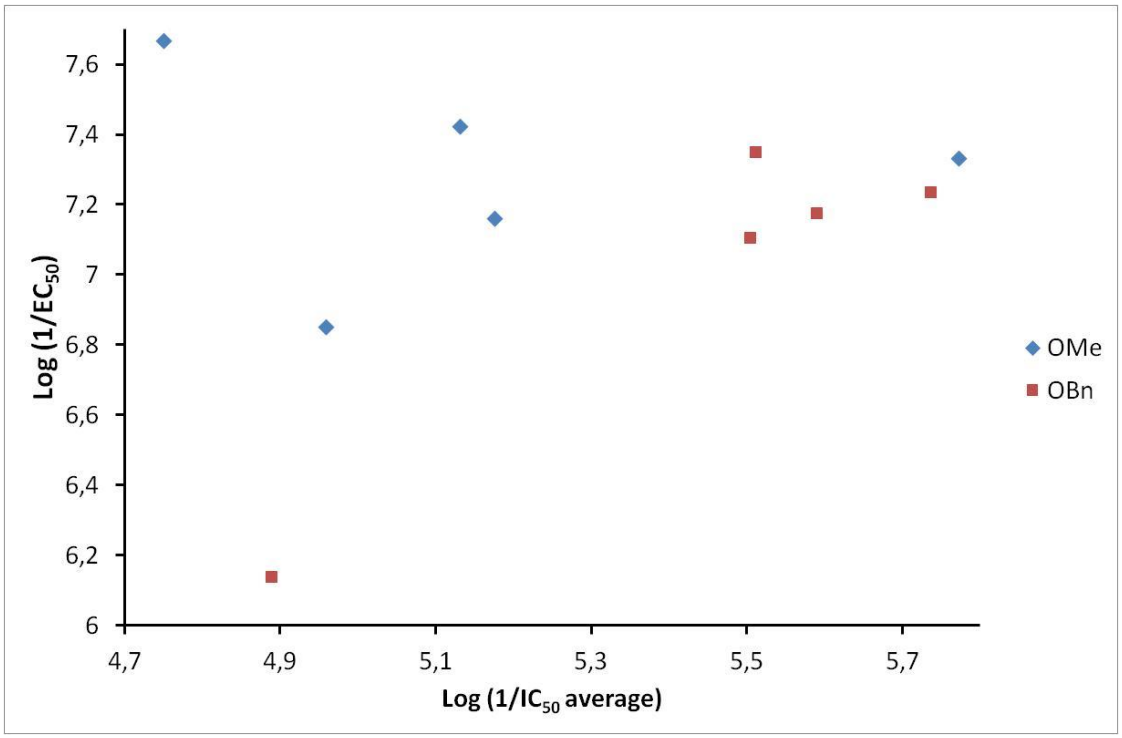

Figure S107: Representation of Log ($1/EC_{50}$) vs Log ($1/IC_{50}$). EC_{50} values corresponded to the Cl^-/NO_3^- antiport process. IC_{50} values corresponded to the average of IC_{50} values for the two cancer lines examined.

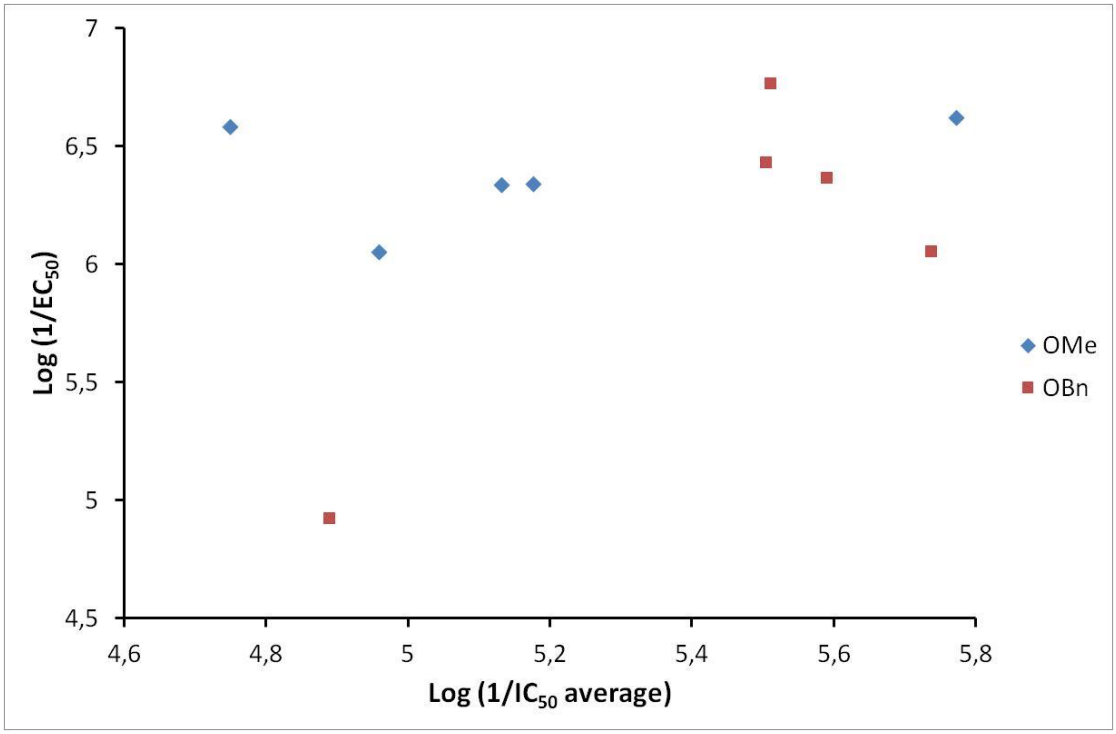

Figure S108: Representation of Log ($1/EC_{50}$) vs Log ($1/IC_{50}$). EC_{50} values corresponded to the Cl^-/HCO_3^- antiport process. IC_{50} values corresponded to the average of IC_{50} values for the two cancer lines examined.