Structurally simple lipid bilayer transport agents for chloride and bicarbonate

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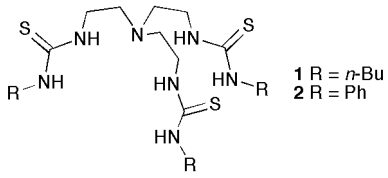
Abstract: A new series of structurally simple compounds containing thiourea groups have been shown by a combination of ion-selective electrode and ^{13}C NMR techniques to be potent chloride-bicarbonate exchange agents that function at low concentration in POPC and POPC/cholesterol membranes.

Introduction

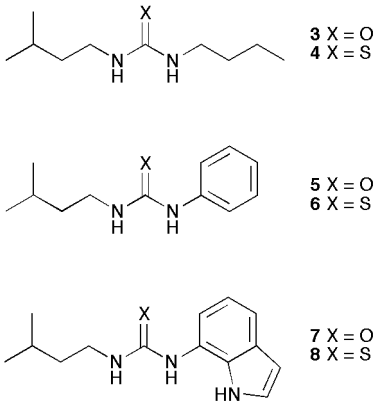
Anion transport[1] is key to many biological processes. Mis-regulation of the transport of chloride across cell membranes can lead to diseases such as cystic fibrosis (caused by the reduction or absence of conductance across epithelial cell membranes as a consequence of a mutation in the CFTR anion channel), Bartter's syndrome and Dent's disease (resulting from mutations in genes which encode for chloride or salt transport channels in renal cells).[2] Similarly misregulation of bicarbonate transport has also been implicated in cystic fibrosis[3] and other diseases.[4] Consequently a number of groups have developed synthetic anion channels and discrete molecular carriers to transport chloride across lipid bilayer membranes.[5] Our interests have recently focused on the development of small molecules capable of chloride/bicarbonate antiport.[6,7]

Ureas and thioureas form stable complexes with oxo-anions and have been employed in a wide variety of receptors for these species.[8] We have recently shown that tris(2-aminoethyl)amine (tren) based tris-thioureas **1** and **2** function as potent chloride/bicarbonate antiport agents in POPC liposomes.[9] Tren-based tris-amides were first shown to bind anions such as chloride by Reinhoudt and co-workers,[10] whilst tren-based ureas have been shown by Custelcean and co-workers[11] and Ghosh and co-workers[12] and others to be effective hosts for oxo-anions whilst the transport properties of tren-based anion receptors have been investigated by DK. Smith and co-workers in U-tube experiments,[13] J.T. Davis and co-workers in lipid bilayers [14] and their flippase activity in lipid bilayers by B.D. Smith and co-workers.[15] In our studies we found that thioureas were significantly more effective transporters than analogous ureas. In previous work A.P. Davis and co-workers have shown that a simple 4-nitrophenylurea when pre-incorporated into a lipid bilayer functions as a chloride transporter at concentrations of transporter/lipid of 1:150.[16] B.D. Smith and co-workers have incorporated urea groups into phospholipids and shown that these compounds function as anion transporters by a relay mechanism in which one functionalised lipid 'hands' the anion over to another in the opposite leaflet.[17] Hence we decided to study a series of very simple thiourea based compounds and compare their anion transport activity to analogous ureas, amides and thioamides. The results show that very simple compounds containing thiourea groups, without pre-incorporation into a lipid bilayer, function as potent chloride/bicarbonate antiport agents at relatively low concentrations.



Results and Discussion

We decided to study a series of ureas and thioureas that had one common side chain and one substituent that would vary across the series. We chose the *iso*-pentyl side chain as the common substituent in these compounds as our previous studies had shown that 4,6-dihydroxyisophthalamides with this substituent were particularly effective membrane transporters.[6] Each compound was then prepared as the urea and thio urea derivative with either n-butyl-, phenyl- or 7-indolyl substituents to study the effects of changing the electronics of this substituent and also the effect of adding an additional hydrogen bond donor group. Indoles have recently been employed in a variety of effective anion receptors and anion-templated foldamers.[18] Compounds **3** – **6** were prepared by reaction of either phenyl or butyl isocyantate or isothiocyanate in dichloromethane or chloroform with *iso*-pentylamine affording the compounds in 49, 49, 72 and 48% respective yields. Compound **7** was prepared by reduction of 7-nitroindole to the amine and then reaction with CDI to afford an activated intermediate which was then coupled to *iso*-pentylamine affording the product in 44% overall yield. Compound **8** was prepared by reaction of 7-aminoindole with thiophosgene to afford the isothiocyanate that was then coupled with *iso*-pentylamine to afford the product in 24% overall yield.



Proton NMR titrations were used to determine the stability constants of compounds **3**-**8** with chloride and nitrate (added as tetrabutylammonium salts) and bicarbonate (added as the tetraethylammonium salt) in DMSO-d_6/0.5% water solution using the WinEQNMR computer program.[19] The results (shown in Table 1) show that the compounds do not detectably interact with nitrate in this solvent mixture but do bind chloride with the indole-based compounds showing the highest affinity for this anion (and in particular the urea derivative). Similarly bicarbonate is bound most strongly by the indole urea followed by the indolylthiourea.

In order to study the chloride transport properties of compounds **3-8** we prepared a series of unilamellar 1-palmitoyl-2-oleoylphophatidylcholine (POPC) vesicles loaded with sodium chloride (489 mM) and suspended them in an external $NaNO_3$ (489 mM) solution. A sample of the receptor (2% molar carrier to lipid) was added as a DMSO solution and the resultant chloride efflux monitored using a chloride selective electrode.[20] After 300 s, the vesicles were lysed by addition of detergent and the final reading of the electrode was used to calibrate 100% release of chloride. The results show that the compounds containing urea groups show no significant release of chloride under these conditions. Compound **6** the phenylthiourea shows moderate activity whilst the butylthiourea and the indolylthiourea both efficiently release chloride from the vesicles. The EC_{50} values for the compounds are shown in Table 2. Transport experiments were repeated in vesicles composed of POPC/cholesterol 70:30 and showed a slightly reduced rate of transport for the thiourea compounds – evidence that these species are functioning as carriers rather than forming channels (ESI Figures S29-31). It is notable that the performance of the thiourea compounds in the POPC/cholesterol membrane is still excellent as this mixture more closely mimics biological cell membranes.

Table 1. Stability constants (K_a/M^{-1}) for compounds **3-8** with anionic guests in DMSO-d_6/0.5% water solution at 298K. All errors are < 15%. Stability constants were calculated following the shift of the *iso*-pentyl NH group.

Compounds	$NO_3^{-[a]}$	$Cl^{-[a]}$	$HCO_3^{-[b]}$
3	[c]	< 10	18
4	[c]	10	58
5	[c]	21	135
6	[c]	22	343[d]
7	[c]	96	1170
8	[c]	28	516

[a] Added as the tetrabutylammonium salt. [b] Added as the tetraethylammonium salt. [c] No interaction observed. [d] NH resonances broaden considerably during this titration

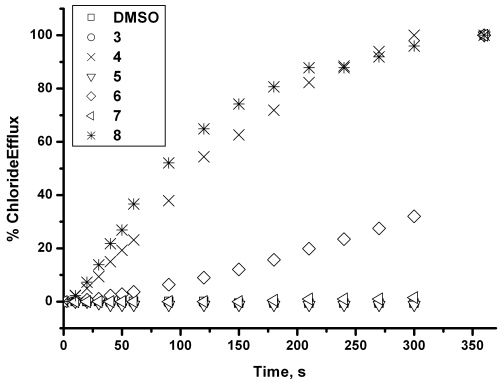


Figure 1 Chloride efflux promoted by 0.02 molar equiv of receptors **3-8** from unilamellar POPC vesicles loaded with 489 mM NaCl buffered to pH 7.2 with sodium phosphate salts. The vesicles were dispersed in 489 mM $NaNO_3$ buffered to pH 7.2 with 5 mM sodium phosphate salts. At the end of the experiment, detergent was added to lyse the vesicles and calibrate the ISE to 100% chloride release. Each point represents the average of three trials.

We had previously shown that tren-based tris thioureas **1** and **2** were potent chloride/bicarbonate antiporters in POPC vesicles. We wished to compare the bicarbonate transport ability of the simpler mono-ureas and mono-thioureas **3-8** with the tren-based tris- ureas **1-2**. Vesicles containing NaCl were prepared and suspended in a solution of Na_2SO_4 and a sample of receptor in DMSO solution was added to this suspension (2% molar carrier to lipid). The negligible release of chloride under these conditions rules out that these compounds function as NaCl or HCl co-transporters to a significant degree. A pulse of bicarbonate was added after 120 s to the external solution. If the compounds function as Cl^-/HCO_3^- antiporters then efflux of chloride should be observed upon addition of the bicarbonate to the external solution. Once again no activity was observed with the urea compounds under these conditions (Figure 2). However, both the butylthiourea **4** and phenylthiourea **6** release chloride from the vesicles under these conditions with the butylthiourea derivative **4** showing slightly faster release of chloride – however the difference in activity of these compounds is significantly less than was observed in the Cl^-/NO_3^- antiport experiments. More active are the tris-thioureas **1** and **2** whilst the most active chloride/bicarbonate antiporter is the

indolylthiourea **8**. It should be noted that in the case of compounds **1** and **2** there are three thiourea groups per receptor and hence the concentration of *thiourea groups* in the experiments with **1** and **2** are three times higher than with compound **8**.

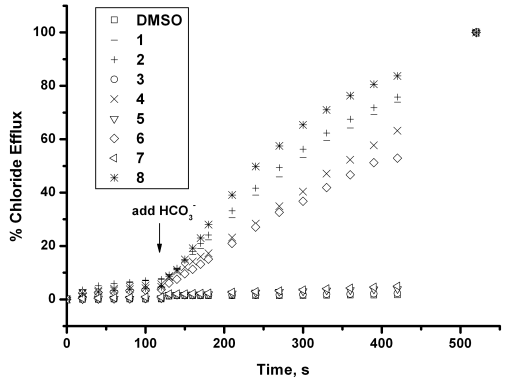


Figure 2 Chloride efflux promoted by 0.02 molar equiv of receptors **1-8** from unilamellar POPC vesicles loaded with 489 mM NaCl buffered to pH 7.2 with 20 mM sodium phosphate salts upon addition of a $NaHCO_3$ pulse to make the extravesicular bicarbonate concentration 40 mM. The vesicles were dispersed in 167 mM Na_2SO_4 buffered at pH 7.2 with 20 mM sodium phosphate salts. At the end of the experiment, detergent was added to lyse the vesicles and calibrate the ISE to 100% chloride release. Each point represents the average of 3 trials.

The data shown in Fig. 2 provided compelling, yet indirect, evidence that the thioureas **4, 6** and **8** are able to promote the transport of bicarbonate across phospholipid membranes. We turned to ^{13}C NMR spectroscopy to gain direct evidence that these thioureas **4, 6** and **8** facilitate transmembrane HCO_3^-/Cl^- exchange (see Fig. 3 and ESI).[6] In these NMR experiments we monitored bicarbonate efflux from vesicles loaded with $H^{13}CO_3^-$ after the addition of compounds **3**-**8**. EYPC vesicles filled with $H^{13}CO_3^-$ and suspended in Na_2SO_4 solution were aged overnight at 4 ºC. Two ^{13}C NMR signals separated by about 1 ppm (δ ~161 and ~160 ppm) were observed, corresponding to signals for intravesicular and extravesicular $H^{13}CO_3^-$ respectively (Fig. 3). No leakage of $H^{13}CO_3^-$ from these vesicles occurred after addition of 50 mM NaCl. A DMSO solution of the transporters was then added to give ligand-to-lipid ratios of 0.04 mol % for **1-8** (see Fig. S91 in the Supporting Information) and ^{13}C NMR spectra were recorded 5 min after addition of compounds **1-8**. As an example of the activity of the thioureas, as compared to the urea analogs see Fig. 3. Thus, thiourea **8** promoted complete $Cl^-/H^{13}CO_3^-$ exchange in 5 min, as confirmed by the observation of only the NMR signal for extravesicular $H^{13}CO_3^-$ (Figure 3). Addition of Mn^{2+} broadened this sharp $H^{13}CO_3^-$ signal at δ 160 ppm into the baseline, confirming that all of the intravesicular $H^{13}CO_3^-$ had been exchanged into the extravesicular solution in the 5 min period. In marked contrast, after addition of the urea analogue **7** the separate signals for intravesicular and extravesicular $H^{13}CO_3^-$ remained relatively unchanged. Addition of Mn^{2+} to this control sample simply erased the smaller extravesicular $H^{13}CO_3^-$ signal, whereas the major intravesicular $H^{13}CO_3^-$ signal remained intact since the paramagnetic Mn^{2+} cannot cross the phospholipid membrane. This ^{13}C NMR data in Fig. 3 was consistent with the ISE data in Fig. 2, which showed that thiourea **8** is a relatively potent anion transporter, whereas the urea analogue **7** is essentially inactive as an anion transporter.

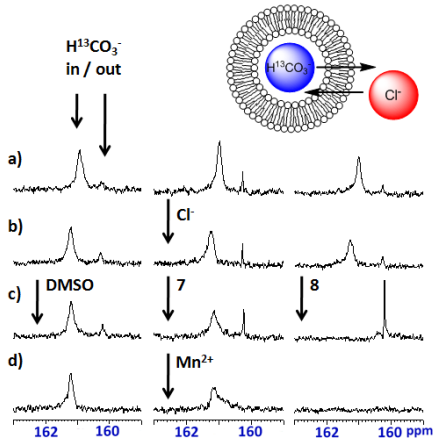


Figure 3 ^{13}C NMR evidence for $H^{13}CO_3^-/Cl^-$ exchange promoted by 0.04 molar equiv of thiourea transporter 8. a) before and b) after addition of a 50 mM NaCl pulse to EYPC vesicles containing 100 mM $NaH^{13}CO_3$ buffered to pH 7.4 with 20 mM HEPES, dispersed in 75 mM Na_2SO_4 buffered to pH 7.4 with 20 mM HEPES; c) 5 min after addition of a DMSO blank, urea 7, or thiourea 8; d) following addition of 0.5 mM $MnCl_2$, a paramagnetic line broadening agent that only affects extravesicular bicarbonate.

The EC_{50} values at 270 s were calculated for the thiourea compounds for chloride release in both the nitrate and bicarbonate antiport systems using Hill analysis (see supplementary information for details). The results are shown in Table 2 together with the initial rates of chloride release for these compounds and are presented with parameters used in the absorption, distribution, metabolism, excretion and toxicity (ADMET) assessment in drug discovery[21] specifically the calculated Ghose-Crippen log P values[22] for compounds **3** – **8** and the polar surface area (PSA) of the compounds both calculated using the Spartan '08 computer program.[23] We reasoned that the parameters that need to be optimised for a compound to be 'drug-like'[24] may correspond to those of an efficient carrier in that the compound would optimally possess both hydrophobic and hydrophilic properties to be capable of extracting an anion from aqueous solution and transporting it across a lipid bilayer. The results show that the thioureas have a higher clog P than the urea analogues and a lower polar surface area. The indolylurea and thiourea have the highest stability constants for bicarbonate from the members of this series and we hypothesise that the activity of the indolylthiourea compound **8** is in part due to a balance of affinity resulting from the geometry and number of hydrogen bond donors in the binding site, higher log P and moderate PSA from amongst this series of compounds. The low EC50

values for compound **8** promoted us to study the chloride transport properties of this receptor at a range of different transporter:lipid loadings in a Cl^-/NO_3^- system. The results show chloride transport activity down to a ratio of 1:25000 transporter:lipid – a remarkable result for such as simple compound not pre-incorporated into the lipid bilayer membrane (Figure 4).

Table 2 EC_{50} values and initial rate of chloride release (% chloride efflux per second) for compounds **4**, **6** and **8** for release of chloride in chloride/nitrate and chloride/bicarbonate systems at 270s. Calculated log P and TPSA ($Å^2$) are also presented for compounds **3** – **8**.

Compounds	EC_{50} at 270s (Cl^-/NO_3^-)	Initial rate of chloride release (Cl^-/NO_3^-) % Cl^- efflux/s at 2% carrier loading	EC_{50} at 270s (Cl^-/HCO_3^-)	Initial rate of chloride release (Cl^-/HCO_3^-) % Cl^- efflux/s at 2% carrier loading	clog P[a]	PSA ($Å^2$)[b]
3	-	-	-	-	1.99	37.0
4	0.1491 %	0.431	0.6049%	0.227	3.14	22.2
5	-	-	-	-	2.42	34.8
6	3.0667 %	0.074	2.7848%	0.188	3.57	21.5
7	-	-	-	-	2.02	44.6-47.7
8	0.02663 %	0.614	0.0405%	0.386	3.16	31.3-35.5

[a] clog P calculated using Spartan '08 for Macintosh (Ghose-Crippen model). [b] Polar surface area (PSA) calculated using Spartan '08 for Macintosh. The receptors were minimised using AM1 semi-empirical methods with the two urea or thiourea NH groups parallel and the PSA and log P values calculated. In the case of the case of the indole containing species two conformations were minimised – one with the indole NH forming a convergent array with the urea NH groups and the other with the indole NH oriented towards the urea or thiourea O or S atom (hence a range of values for PSA are given).

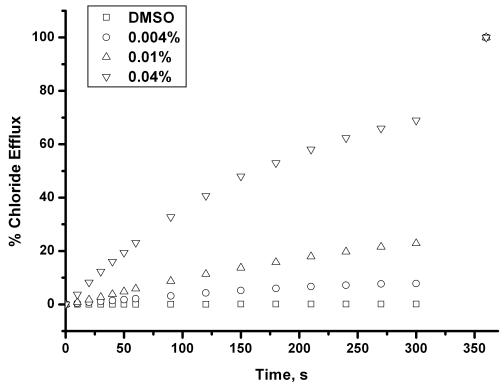
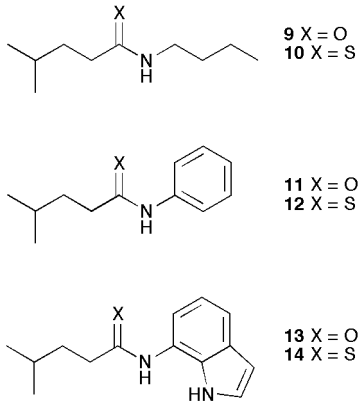


Figure 4 Chloride efflux promoted by 0.00004, 0.0001, and 0.0004 molar equiv of receptor **8** from unilamellar POPC vesicles loaded with 489 mM NaCl buffered to pH 7.2 with sodium phosphate salts. The vesicles were dispersed in 489 mM $NaNO_3$ buffered to pH 7.2 with 5 mM sodium phosphate salts. At the end of the experiment, detergent was added to lyse the vesicles and calibrate the ISE to 100% chloride release. Each point represents the average of three trials.

We also prepared a series of amides and thioamides with analogous structures to the series of ureas and thioureas. The transport ability of these compounds (**9-14**) was studied using under the same conditions as the ureas and thioureas for chloride/nitrate antiport. The results (Figure 5) show a much diminished chloride transport ability for thioamides **10** and **14** as compared to thioureas **4** and **8**.



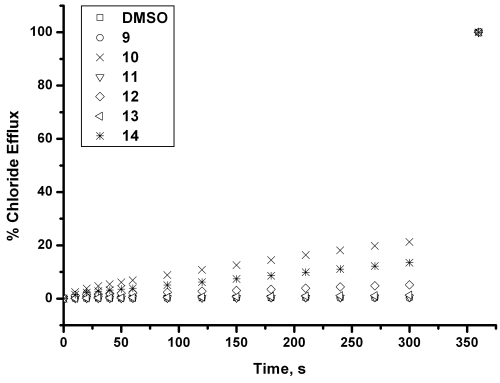


Figure 5 Chloride efflux promoted by 0.02 molar equiv of receptors **9-14** from unilamellar POPC vesicles loaded with 489 mM NaCl buffered to pH 7.2 with sodium phosphate salts. The vesicles were dispersed in 489 mM $NaNO_3$ buffered to pH 7.2 with 5 mM sodium phosphate salts. At the end of the experiment, detergent was added to lyse the vesicles and calibrate the ISE to 100% chloride release. Each point represents the average of three trials.

Conclusion

A series of simple ureas and thioureas have been synthesised and their anion transport properties studied by a combination of ion-selective electrode and ^{13}C NMR techniques. The results show that very simple thiourea compounds such as **4**, **6** and **8** are capable of chloride/bicarbonate antiport with compounds **4** and **8** possessing the highest transport efficiency. Analogous amides and thioamides have greatly diminished anion transport abilities. The 'champion' of this series, compound **8**, combines a higher clogP and lower polar surface area than its urea analogue, which is inactive as a chloride/bicarbonate antiport agent, with a convergent array of three hydrogen bond donors. This results in remarkably potent anion transport properties for such as simple

compound. The goal of using small molecules as treatments for diseases caused by misregulation of chloride transport, such as cystic fibrosis, will be brought closer when compounds designed as membrane transporters have optimised ADMET properties. Conversely by optimising ADMET properties we may at the same time improve the anion transport properties of these species (with the caveat that unlike small molecule drugs, we wish the compound to remain in the membrane and not diffuse through it).

Notes and references

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† Electronic Supplementary Information (ESI) available: Synthetic procedures, NMR spectra, anion transport studies, crystal structures of compounds **5** and **8** . See DOI: 10.1039/b000000x/

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