Journal Name

ARTICLE

1,8-Diamidocarbazoles: an easily tuneable family of fluorescent anion sensors and transporters

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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The synthesis, structure and anion recognition properties of an extensive, rationally designed series of bisamide derivatives of 1,8-diaminocarbazole and 1,8-diamino-3,6-dichlorocarbazole are described. Despite simple structures and the presence of only three hydrogen bond donors, such compounds are remarkably strong and selective receptors for oxyanions in DMSO+0.5%H_2O. Owing to their carbazole fluorophore, they are also sensitive and selective turn-on fluorescent sensors for $H_2PO_4^-$, with a more than 15-fold increase in fluorescence intensity upon binding. Despite relatively weak chloride affinity, some of the diamidocarbazoles have also been shown, for the first time, to be very active chloride transporters through lipid bilayers. The binding, sensing and transport properties of these receptors can be easily modulated by the usually overlooked variations in the length and degree of branching of their alkyl side arms. Overall, this study demonstrates that the 1,8-diamidocarbazole binding unit is a very promising and synthetically versatile platform for the development of fluorescent sensors and transporters for anions.

Introduction

The design of artificial receptors that strongly and selectively bind anions is one of the greatest challenges in supramolecular chemistry, especially when binding in aqueous solutions is concerned.[1] This is due to the importance of anions in many chemical, biological, medicinal and environmental processes as well as the inherent difficulties associated with this endeavour. The significance and difficulties of anion recognition arise, in large part, from the vast structural and functional diversity of anions, which span the range from simple inorganic ones (spherical Cl^-, linear CN^-, trigonal NO_3^-, tetrahedral SO_4^{2-}, etc.), through myriad organic (and often chiral) anionic metabolites, to proteins and DNA.

Nevertheless, progress in the design and synthesis of anion receptors has set the stage for rapid development of this field towards multiple applications such as anion sensing,[2] anion templated synthesis,[3] anion-responsive materials[4] and supramolecular catalysis,[5] just to name a few of the most actively pursued sub-fields of this increasingly diverse area.

For example, anion templation has been developed as a reliable tool for the synthesis of many intricate structures, such as catenanes, rotaxanes, cages, helicates, and others.[6] Another area of intense current interest is the development of synthetic anionophores - molecules capable of facilitating transmembrane anion transport.[7,8] Since anion transport through lipid bilayers is critical for many cellular functions, anionophores are likely to be biologically active. For instance, disruption of homeostasis and intracellular pH levels can lead to apoptosis in cancer cells.[9] Furthermore, anionophores hold promise in the development of novel treatments against diseases related to malfunction of anion transport in cells, such as cystic fibrosis, Best disease and Bartter's syndrome.[8,9]

The progress in the construction of anion receptors has primarily been the result of the development of relatively simple organic building blocks that exhibit strong affinities towards anions.[10] Fundamental knowledge about their precise structure, conformational preferences, anion affinities etc., allow chemists to successfully construct anion receptors with targeted affinities, selectivities and sensitivities.

In 2004, Chmielewski et al. developed a particularly promising building block for the construction of anion receptors – 1,8-diamino-3,6-dichlorocarbazole **1** (DADCC, Chart 1).[11] It combines several attractive features, such as ease of synthesis and derivatization, the presence of a strong hydrogen bond donor – carbazole NH, and a rigid skeleton facilitating preorganization of hydrogen bond donors. Moreover, direct coupling of its anion binding site with a carbazole chromophore/fluorophore enables efficient anion sensing by UV-Vis and fluorescence spectroscopies. A particularly appealing feature of DADCC **1** is that it could be easily converted into many different families of hydrogen bonding receptors such as amides, thioamides, ureas, thioureas, sulfonamides or guanidines, of which only a few amides and ureas have been described thus far. Although the first simple bisamide derivatives of DADCC **1** had the same number and geometry of hydrogen bond donors as the pyrrole bisamides **2** (Chart1),[12,13] the carbazole derivatives bind

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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

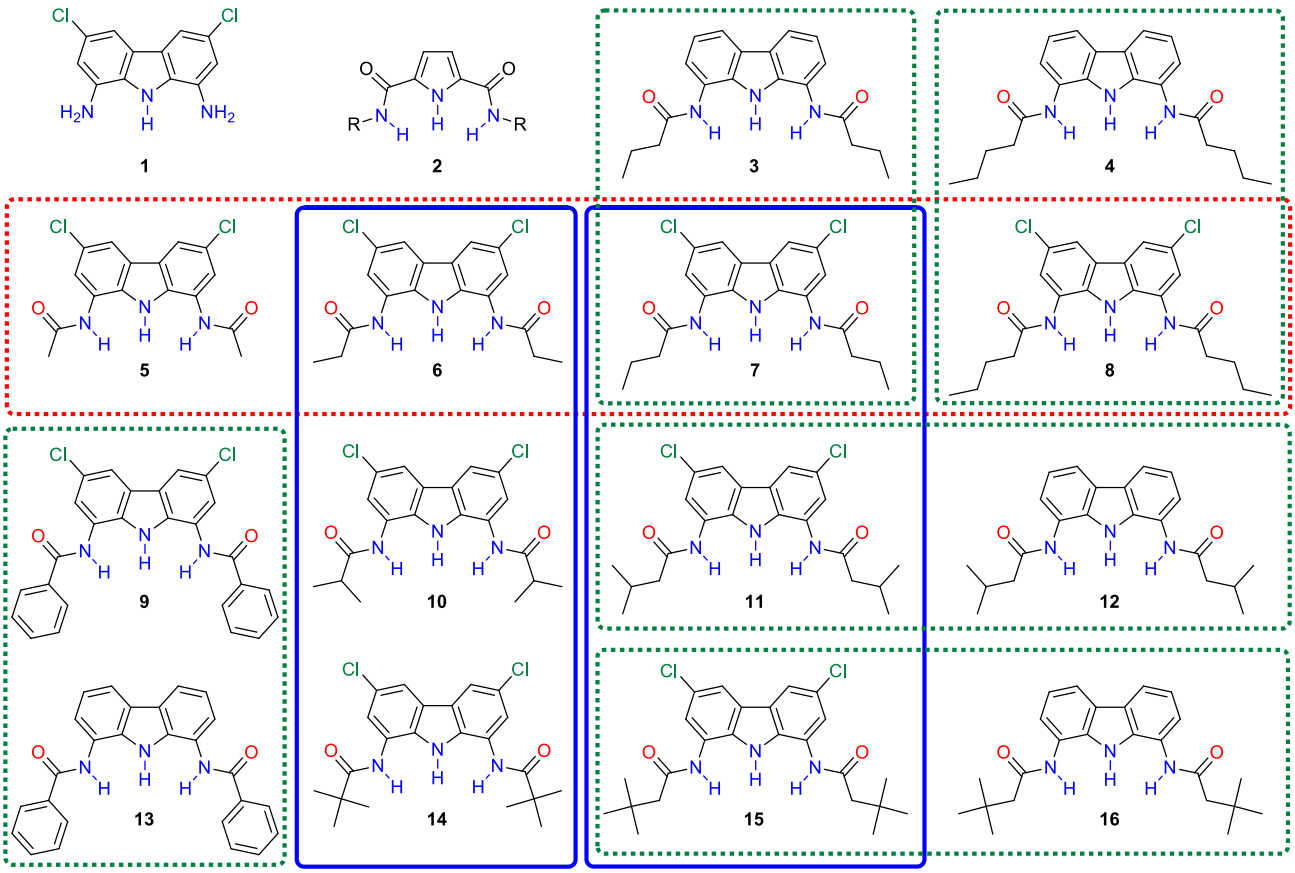


Chart 1 Structural relationships within diamidcarbazole family discussed in this paper: pairs of chlorinated and non-chlorinated receptors are encircled by a green dotted line, receptors differing in the length of their alkyl chains are marked by a red dotted line and the receptors differing with the degree of branching – by a blue solid line.

carboxylates by at least 2 orders of magnitude better than pyrrole bisamides in a very competitive solvent mixture: DMSO+0.5%H_2O.

Although the DADCC motif has been successfully used by us[14,15] and other research groups[16-20] to construct potent anion receptors and sensors, the full potential of this building block remains largely unexplored. For instance, the ability of diamidocarbazoles to facilitate transmembrane anion transport has never been investigated thus far. Also, we have recently shown that diamidocarbazoles show promise as building blocks for the anion templated synthesis of interlocked structures.[15]

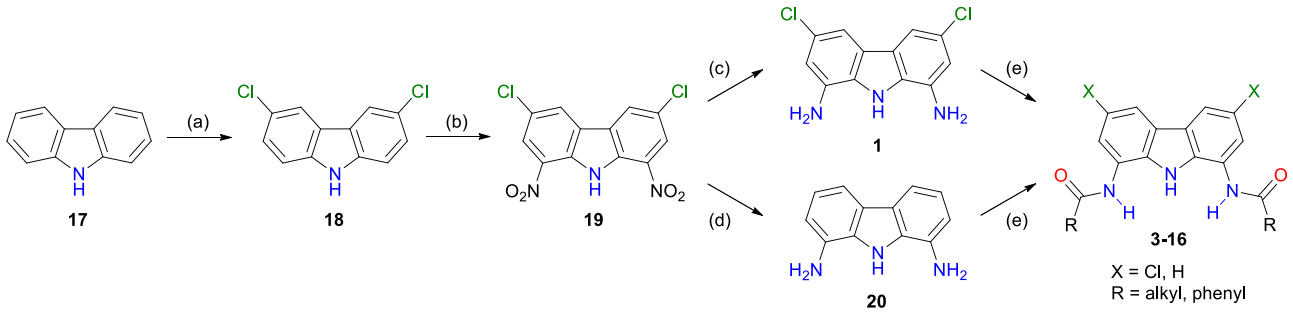
Thus, in the present contribution we present results from our systematic investigation into the anion binding, sensing and transport properties of a rationally designed series of 1,8-diamidocarbazole derivatives. The impact of both amide substitution and chlorination of the aromatic skeleton is examined. As a result, we have identified potent anion sensors and transmembrane carriers. Synthetic versatility and easy tuneability make these receptors highly promising lead structures for further development of more complex anion sensors and transporters with improved properties as well as for the construction of interlocked structures. The results of our systematic structure-properties relationship studies presented below serve to pave the way in this direction.

Results and discussion

Design and synthesis of model receptors

To study the influence of various structural factors on the anion binding, sensing and transport properties of diamidocarbazoles, we have designed and synthesized a family of fourteen receptors **3**-**16**, varying in substitution of their carbazole core (Cl vs. H) as well as in the nature (aromatic vs. aliphatic), length, and degree of branching of their amide side arms (Chart 1). There is compelling evidence for a crucial role of well-balanced anion affinity and lipophilicity in anion transport, and some recent studies show that the variation of the length of alkyl side chains has a profound effect on the rate of anion transport.[21] However, the effect of branching of aliphatic side chains on anion coordination and transport is less explored, despite its potential role in the preparation of chiral anion binding pockets.

The key substrates for the synthesis of diamidocarbazoles, diamines **1** and **20**, were prepared in three steps from carbazole according to Scheme 1. First, carbazole was selectively chlorinated in positions 3 and 6 by treatment with sulfuryl chloride in CH_2Cl_2 at room temperature. The desired 3,6-dichlorocarbazole **18** was isolated in 60% yield by filtration and washing with hot hexane.[11] Once the two most reactive positions of the carbazole moiety were blocked by chlorination, subsequent nitration of **18** with 100% nitric acid



Scheme 1 The synthesis of 1,8-diamidocarbazole receptors **3**-**16**. (a) SO_2Cl_2, CH_2Cl_2, RT, 60%. (b) HNO_3 (100%), $(AcO)_2O$/AcOH, 1 °C to 110 °C, 73%, (c) H_2 (balloon), 5%Pt(S)/C (cat.), CH_3CN, RT, 90%. (d) NH_2NH_2, 10%Pd/C (cat.), EtOH, reflux, 6 h, 75%. e) RCOCl, Et_3N, CH_3CN, RT, 40-88%.

in AcOH/$(AcO)_2$ mixture smoothly gave 3,6-dichloro-1,8-dinitrocarbazole **19** in 73% yield.[11] Hydrogenation of **19** is often accompanied by partial dechlorination, which leads to an inseparable mixture of amines. This problem was originally solved by using dry acetonitrile as a reaction medium,[11] but recently we have found that the results depend on the particular batch of a Pd/C catalyst. We screened several other platinum and palladium catalysts and found that the commercially available deactivated catalyst Pt(S)/C is more practical, yielding 93% of pure **1** in just 4.5 h (see ESI).

The unsubstituted 1,8-diaminocarbazole **20** was obtained in a one-pot reduction and dechlorination of the 3,6-dichloro-1,8-dinitrocarbazole **19**.[22,23] Thus, both **1** and **20** are now easily available on a multigram scale using inexpensive reagents and chromatography-free methods

Unfortunately, subsequent acylation of the diamines with various acyl chlorides according to the original method[11] was often accompanied by the formation of persistent impurities. Since most of the desired diamidocarbazoles are very poorly soluble in common organic solvents (except for DMSO, DMF, and aprotic solutions of tetrabutylammonium salts), their chromatographic purification is impractical. Attempts to purify them by crystallization also failed, giving low yields and unsatisfactory purity of poorly crystalline samples. Thus, we have carefully optimized the reaction conditions in order to minimize both the monoacylation and over-acylation (imide formation), the major sources of poorly soluble and difficult to separate side products. The key to success was adding the amines to the solution of a corresponding acid chloride, favouring rapid formation of bisamides, which precipitate from the reaction mixture. Using this procedure, we managed to obtain pure receptors after simple filtration and washing, in good to moderate yields.

Structural studies

Two model receptors were investigated by X-ray crystallography: **4**, with aliphatic side arms, and **13**, with aromatic side arms. Diffraction-grade single crystals of both were obtained by slow diffusion of Et_2O into a solution of a receptor in a 9:1 CH_2Cl_2/CH_3OH solvent mixture.

Both compounds adopt very similar conformations in the solid state, with both amide NHs pointing away from the central carbazole NH. Such a divergent, *anti-anti* conformation

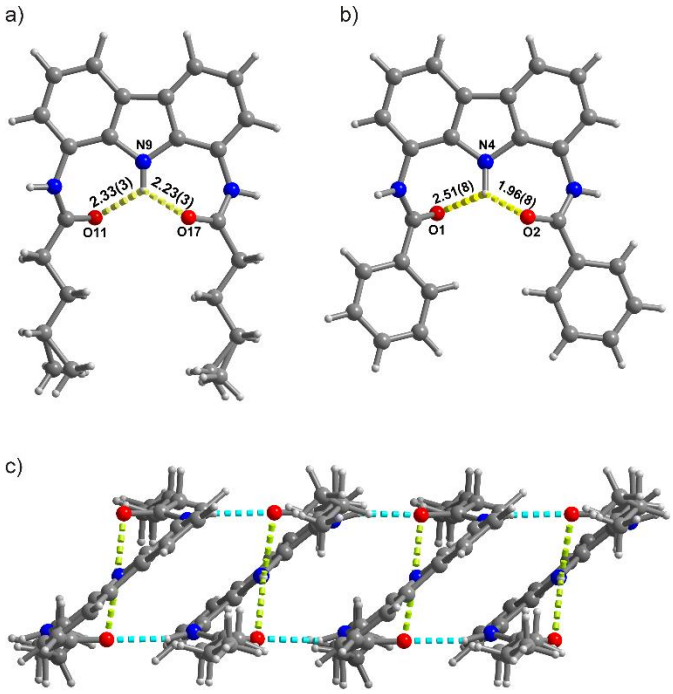


Figure 1 X-ray crystal structures of a) **4**, b) **13** and c) crystal packing of **4**.

is stabilized by two short intramolecular hydrogen bonds between amide oxygen atoms and the carbazole NH (Figure 1). As a result, the anion binding cavity is closed, and in this conformation the molecules would not be able to bind anions, except for weak, external complexes stabilized by a single hydrogen bond.

The side view reveals that the amide side groups are not coplanar with the carbazole skeleton, but rather tilted by 36-50° in such a way that each amide NH is located on the opposite side of the carbazole plane (Figure 2c). This allows them to form additional hydrogen bonds with neighbouring molecules, which leads to the formation of a solid state 1D supramolecular polymer. Apart from these peptide-like hydrogen bonds, the polymer is also additionally stabilized by π-π stacking interactions between carbazole planes. These findings help to rationalize the very poor solubility of diamidocarbazole receptors in both aprotic solvents, which are unable to break strong hydrogen bonds, and protic solvents, such as methanol, which are unable to break π-π interactions.

Table 1. Association constants K_a [M^{-1}] and logarithms of association constants (in brackets) of carbazole receptors **3**-**16** with various anions in DMSO+0.5%H_2O(w/w). Estimated errors are <15% (see ESI for details).

Receptor	$H_2PO_4^-$ [a]	$PhCOO^-$ [a]	Cl^- [b]
3	1.41×10^4 (4.15)	3.00×10^3 (3.48)	42 (1.62)
5	1.21×10^5 (5.08)	7.55×10^3 (3.88)	75 (1.88)
6	9.86×10^4 (4.99)	1.08×10^4 (4.03)	104 (2.02)
7	9.62×10^4 (4.98)	1.60×10^4 (4.20)	109 (2.04)
8	9.40×10^4 (4.97)	1.34×10^4 (4.13)	111 (2.05)
9	6.98×10^3 (3.84)	1.79×10^3 (3.25)	14 (1.15)
10	1.21×10^5 (5.08)	1.31×10^4 (4.12)	131 (2.12)
11	9.68×10^4 (4.99)	2.18×10^4 (4.34)	123 (2.09)
12	1.10×10^4 (4.04)	4.43×10^3 (3.65)	42 (1.62)
13	1.66×10^3 (3.22)	573 (2.76)	< 10 (< 1)
14	4.71×10^3 (3.67)	2.01×10^3 (3.30)	56 (1.75)
15	8.32×10^4 (4.92)	2.90×10^4 (4.46)	159 (2.20)
16	1.02×10^4 (4.01)	4.65×10^3 (3.67)	48 (1.68)

[a] Determined by UV-vis titrations. [b] Determined by ^{1}H NMR titrations.

3) Benzamide derivatives **9** and **13** show a much lower affinity for anions than their aliphatic analogues. This might be surprising in view of the generally higher hydrogen bond donating ability of aromatic amides[27] as well as the additional CH---O hydrogen bonding interactions[24] between the amide phenyl rings and benzoate anion observed in the X-ray crystal structure of **13**×$PhCOO^-$. We hypothesize that the aromatic side arms pay a higher energetic penalty for breaking the intramolecular hydrogen bonds in the unbound receptor and also for the adoption of a non-planar binding conformation.

4) Additional substituents α or β to the carbonyl group do not impact anion binding significantly, as long as there is at least one hydrogen atom α to the C=O group. Unfortunately, they do not significantly improve solubilities either. On the contrary, receptor **14**, with a quaternary *α* carbon atom, has markedly reduced anion affinity and greatly improved solubility in common organic solvents. These traits are likely due to the bulky *t*-Bu substituents, which hamper both anion binding and the formation of intermolecular hydrogen bonds in the solid state.

The *t*-Bu groups β to the amide C=O increase the solubility enough to facilitate purification and anion binding studies. This, together with uncompromised anion binding properties, make receptors **15** and **16** the best candidates for further studies.

5) Chlorinated receptors with aliphatic side arms (except for the most sterically congested **14**) show remarkable affinity for $H_2PO_4^-$, with logK values in the range of 4.92-5.08. Within this sub-group, receptor **5** binds dihydrogen phosphate particularly strongly and selectively - 16 times more strongly than $PhCOO^-$ and more than 1600 times more strongly than chloride. On the other hand, **15** seems to be the best leading structure for the development of receptors for carboxylates – it binds $PhCOO^-$ most strongly, with K = 29000 M^{-1}, which is only ~3 times less than for $H_2PO_4^-$ and >160 times more than for Cl^-.

Fluorescence sensing

To compare the fluorescent sensing properties of 3,6-dichloro substituted and unsubstituted carbazole receptors, the two *t*-$BuCH_2$- bearing derivatives **15** and **16** were investigated. The chlorinated compound **15** has two absorption maxima, at 349.5 and 362.5 nm and fluorescence maximum at 390.5 nm in DMSO+0.5%H_2O. The respective maxima for the 3,6-unsubstituted compound **16** are blue shifted by approximately 12.5-15.5 nm (Figure 4), with the intensity of the fluorescence of **16** about 70% higher than that of **15**. It shows that the spectroscopic properties of diamidocarbazoles can be conveniently modulated by varying substituents on the carbazole core.

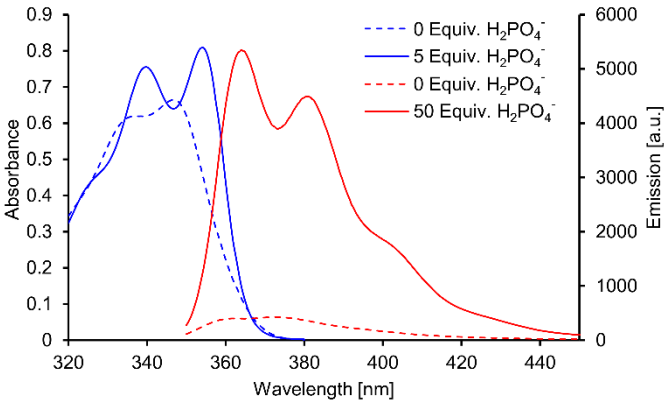


Figure 4 UV-Vis absorption (blue lines) and emission (red lines, excitation at 335 nm) spectra of **16**

Both compounds display bright near-ultraviolet to visible emission in DMSO+0.5%H_2O solution upon irradiation at 350.5 and 340 nm for **15** and **16** respectively. The fluorescence of 3,6-dichloro substituted receptor **15** increased by a factor of 2 upon addition of $H_2PO_4^-$ in DMSO+0.5%H_2O while significant decrease was observed upon addition of $PhCOO^-$ and only minor changes were observed after the addition of Cl^- (see the ESI). Much more pronounced fluorescence turn-ON effect was seen for the 3,6-unsubstituted receptor **16**: *ca.* 15-fold increase in fluorescence due to $H_2PO_4^-$ (Figure 4) with only slight increases for $PhCOO^-$ and Cl^-. Thus, the intrinsic binding selectivity of diamidocarbazoles ($H_2PO_4^-$>$PhCOO^-$>>Cl^-) is greatly amplified by selective fluorescence turn-ON response to dihydrogen phosphate. As a result, both compounds **15** and **16** behave as selective turn-ON fluorescent sensors for dihydrogen phosphate and work well even in the presence of large excess of chloride (see ESI). Importantly, no traces of deprotonation could be seen in any of these spectra.

Transmembrane anion transport

The potential of diamidocarbazoles to serve as anion transporters had not been previously investigated. To assess it, model phospholipid vesicles composed of 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) were used as convenient model systems. These vesicles can be prepared with good control of size and encapsulated contents. Chloride efflux from NaCl-loaded vesicles can be monitored using a chloride selective electrode since encapsulated chloride is not detected by the electrode. At the beginning of the experiment a suspension of vesicles in an isotonic $NaNO_3$ solution is spiked with a DMSO solution of a receptor. Accordingly, the assay verifies not only the anion transport ability of the receptors but also their ability to incorporate into the phospholipid membrane, which is particularly relevant to potential medicinal applications. Addition of detergent at the end of the experiments to disrupt the membrane and release all of the encapsulated chloride allowed the data normalization to a final 100% chloride concentration.

Using this assay, we first investigated all receptors at a 10 µM concentration, which corresponded to a 2% carrier:POPC molar ratio. Those results are shown in Figure 5.

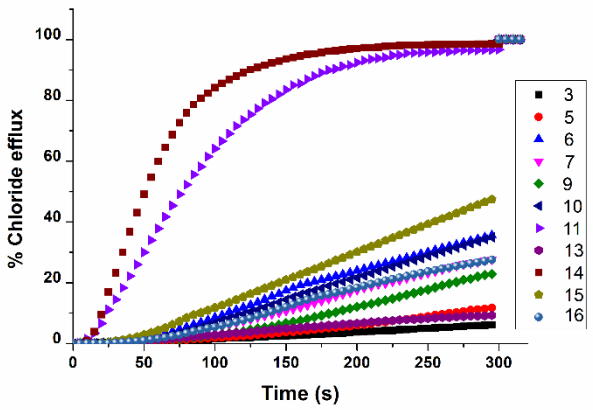


Figure 5. Chloride efflux promoted by carbazole derivatives **3**-**16** (10 µM, 2 % mol carrier to lipid concentration) in unilamellar POPC vesicles. Vesicles were loaded with 489 mM NaCl buffered at pH 7.2 with 5 mM phosphate and dispersed in 489 mM $NaNO_3$ buffered at pH 7.2. Each trace represents the average of at least three trials.

Significant activity was observed for several compounds, with derivatives **11** and **14** being the most active. Chlorination of the carbazole moiety had a positive impact on the transport activity, as comparisons between analogous chlorinated and non-chlorinated derivatives clearly showed. Benzamide derivatives were almost inactive under these conditions, similarly to the results of the anion coordination studies. The activity of receptors with aliphatic side arms strongly depends on subtle structural variations. For example, consecutive additions of methyl groups β to the amide group result in a sharp increase in activity from **7** to **11**, followed by sudden drop from **11** to **15**. Similarly, the addition of a single methyl group α to CONH converts moderately active **10** into the most active **14**. These observed activity trends are likely due to a combination of several factors which makes interpretation and predictions difficult. It is necessary therefore to screen large libraries of receptors in a search for compounds with desired activity. The synthetic versatility of diamidocarbazoles would be an asset in such an endeavour.

The transport activity of the most active compounds **11** and **14** was further studied at different concentrations (Fig. S5.1-S5.7 in ESI). These compounds facilitated chloride efflux in a concentration dependent manner. This allowed us to calculate an EC_{50} value, which represents the amount of compound needed to induce the outflow of half of the encapsulated chloride during these assays (300 s). The calculated values were 0.184 and 0.097 µM respectively for **11** and **14**.

To shed some light on the mechanism of action and investigate the ability of these compounds to facilitate the transport of other anions, we then suspended the vesicles in an isotonic sulphate medium. Under these conditions, no significant chloride efflux was detected. This agrees with an anion exchange mechanism for the transport activity elicited by these compounds and shows that the transport of the dinegative and extremely hydrophilic sulphate ion is negligible under these conditions. On the other hand, the addition of bicarbonate to the external medium switched ON the chloride efflux, suggesting that the diamidocarbazoles promote the influx of HCO_3^-. This, together with the very high oxyanion affinity of the diamidocarbazoles, bodes well for future development of oxyanion transporters. Similar to the results presented above, compound **14** was the most active in the Cl^-/HCO_3^- antiport, with a calculated EC_{50} value of 3.35 µM. The higher hydrophilicity of bicarbonate relative to nitrate as well as the different experimental conditions in the chloride efflux assay accounted for the differences in the calculated EC_{50} values.

Summing up, simple structural variations (carbazole core substitutions or amide side arms) readily modulate the transmembrane transport activity of diamidocarbazoles. Our work has identified two very potent derivatives and demonstrated the usefulness of this motif in the development of anion carriers.

Conclusions

1,8-Diamidocarbazoles have been shown to be easily available and easily tuneable family of highly potent receptors, sensors and transporters for anions. Despite simple structures and the presence of only three hydrogen bond donors, they are remarkably strong and selective receptors for oxyanions in DMSO+0.5%H_2O, with affinities reaching $10^{5.1}$ M^{-1} for dihydrogen phosphate and $10^{4.5}$ M^{-1} for benzoate, and selectivities relative to chloride exceeding 1600 ($K_{H_2PO_4^-}/K_{Cl^-}$ ratio) and 180 (K_{PhCOO^-}/K_{Cl^-}). Their X-ray structures suggested that their high selectivities originate, *inter alia*, from a poor geometric match between the relatively small chloride anions and the wide and rigid binding pockets of diamidocarbazoles. Nevertheless, despite their relatively weak chloride affinity, some diamidocarbazoles were active chloride transporters through lipid bilayers, with EC_{50} values as low as 0.1 µM. Easy

deliverability and the fact that some of these compounds can transport bicarbonate anions is particularly interesting in view of the generally high oxyanion affinity of diamidocarbazoles. Due to their carbazole fluorophore, diamidocarbazoles are also very promising building blocks for the development of fluorescent anion sensors. In particular, the 3,6-unsubstituted receptors are sensitive and selective turn-on fluorescent sensors for $H_2PO_4^-$ anions, with a more than 15-fold increase in fluorescence intensity upon binding.

The systematic structure – affinity relationship studies presented in this paper provide several hints for future development of more elaborate carbazole-based receptors, sensors and transporters for anions. First, we found that although the electron withdrawing chlorine substituents in positions 3 and 6 of the carbazole ring increase anion binding constants considerably, (7-9 times for $H_2PO_4^-$, 5-6 times for $PhCOO^-$ and 2-3 times for Cl^-), the chlorine-free receptors show much stronger fluorescence turn-on response to $H_2PO_4^-$ anions. Secondly, aromatic amide residues seem to be detrimental for both anion binding and anion transport abilities as compared to aliphatic amides. Thirdly, variations in the length of alkyl chains and (usually underestimated) degree of branching have a profound influence on anion transport abilities of diamidocarbazoles. Even the addition or removal of a single CH_3 group may be critical for anionophoric activity, although the structure-activity relationship might be obscured here by solubility issues.

Experimental

Synthetic procedures and characterization of ligands, protocols and results of NMR, UV-vis and fluorescence titrations, detailed procedures of anion transport as well as crystallographic data for new X-ray structures are available in Supporting Information.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We thank the Polish National Science Centre for grant OPUS (2011/01/B/ST5/03900). The study was carried out at the Biological and Chemical Research Centre, University of Warsaw, established within a project co-financed by the European Union through the European Regional Development Fund under the Operational Programme Innovative Economy 2007–2013.

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