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Synthesis and anion-binding properties of new disulfonamide-based receptors

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ABSTRACT

The synthesis of disulfonamide receptor scaffolds for anion binding is reported. Acyclic receptors are found to tightly bind acetate in MeCN-d_3 with dominant 1:1 stoichiometry, a smaller, sequential 1:2 (H+G) association is also found. Constraint of the disulfonamide receptor into macrocycles serves to eliminate the 1:2 binding stoichiometry and X-ray crystal structures of several macrocyclic receptors allow rationalisation of their affinity for acetate binding. L-Valine derived macrocycles maintain tight 1:1 binding of acetate ($K_a^{1:1}$ $>10^4$ M^{-1}) in MeCN-d_3 and display preference for oxyanion binding in more competitive MeCN-d_3/2% H_2O.

1. Introduction

The development of synthetic receptors for anions is of considerable interest because of their potential biomedical and environmental applications.[1] In particular, the role of carboxylate as a functional group in many important biological systems has prompted us, and others, to investigate various binding motifs, incorporating multiple hydrogen bond donor sites, for binding carboxylate functionality[2] and there are many recent applications of ureas,[3] thioureas,[4] guanidinium salts,[5] amides,[6] pyrroles[7] and polyamines,[8,9] typically in development of receptors for amino acid and peptide recognition. Several examples of acyclic receptors incorporating sulfonamides for hydrogen-bonded complexation of anionic guests have also been reported.[10] These include a simple disulfonamide receptor, described by Crabtree et al.[10g] (Fig. 1a), which accommodates halide and acetate guests with high association constants in apolar solvents, as a result of the strong hydrogen bond donating ability of sulfonamide NHs, and the receptor flexibility, which allows optimal convergence of hydrogen bond donors with the anion acceptor. We anticipated that tighter anion binding could be achieved using this simple disulfonamide scaffold with incorporation of additional hydrogen bonding (amide) functionality. The simplest structures would incorporate such functionality in an acyclic framework (Fig. 1b). However in earlier work we have described the synthesis and binding properties of 'tweezers' bearing sulfonamidopeptide side arms as receptors for *N*-protected amino acids and peptides[11] and the repeating backbone structure of these receptors contained both strong sulfonamide hydrogen bond donors and amide functionality, which collapsed into an intramolecularly folded structure and demonstrated relatively weak association constants with peptide guests as a consequence of the energetic penalty of unfolding this collapsed conformation. In order to overcome the possibility that substantial reorganisation of an intramolecularly folded receptor of type (b) (Fig. 1) will be required for anion binding, we have also considered constraining such receptors in a macrocyclic framework. Herein we describe studies in which we have sought firstly to prepare acyclic disulfonamides functionalised with additional amide hydrogen bonding donors, and characterised their binding properties with simple carboxylate guests. We have also prepared a series of macrocyclic receptors (Fig. 1c and d), which may also incorporate chirality into the receptor structure with the ultimate objective of preparing receptors for the enantioselective recognition of amino acids.[4c,d,5a,12] Four hydrogen bonding interactions are possible for association with a carboxylate guest molecule and each scaffold possesses the benzene-1,3-disulfonamide moiety derivatised with either diamines (Fig. 1c)[13] or α-amino acids (Fig. 1d).

Macrocyclisation is achieved with a bridging tether, which may incorporate solubilising substituents or be varied in structure and length for optimisation of the cavity size or macrocycle flexibility.

2. Results and discussion

2.1. Synthesis and structure

Two synthetic approaches were adopted for preparation of receptors based upon the benzene-1,3-disulfonamide scaffold, via condensation of benzene-1,3-disulfonyl chloride with either monoprotected bis-amines or with L-valine. Both acyclic (**3**) and macrocyclic (**6**–**9**) bis-amine derived receptors were targeted in order that comparative binding studies could be undertaken to ascertain the effect of conformational constraints on the binding properties of the

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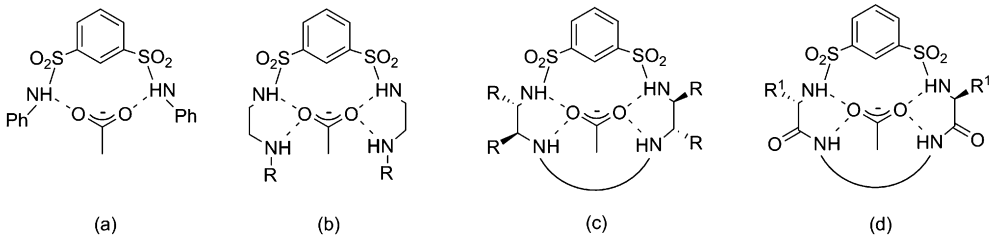
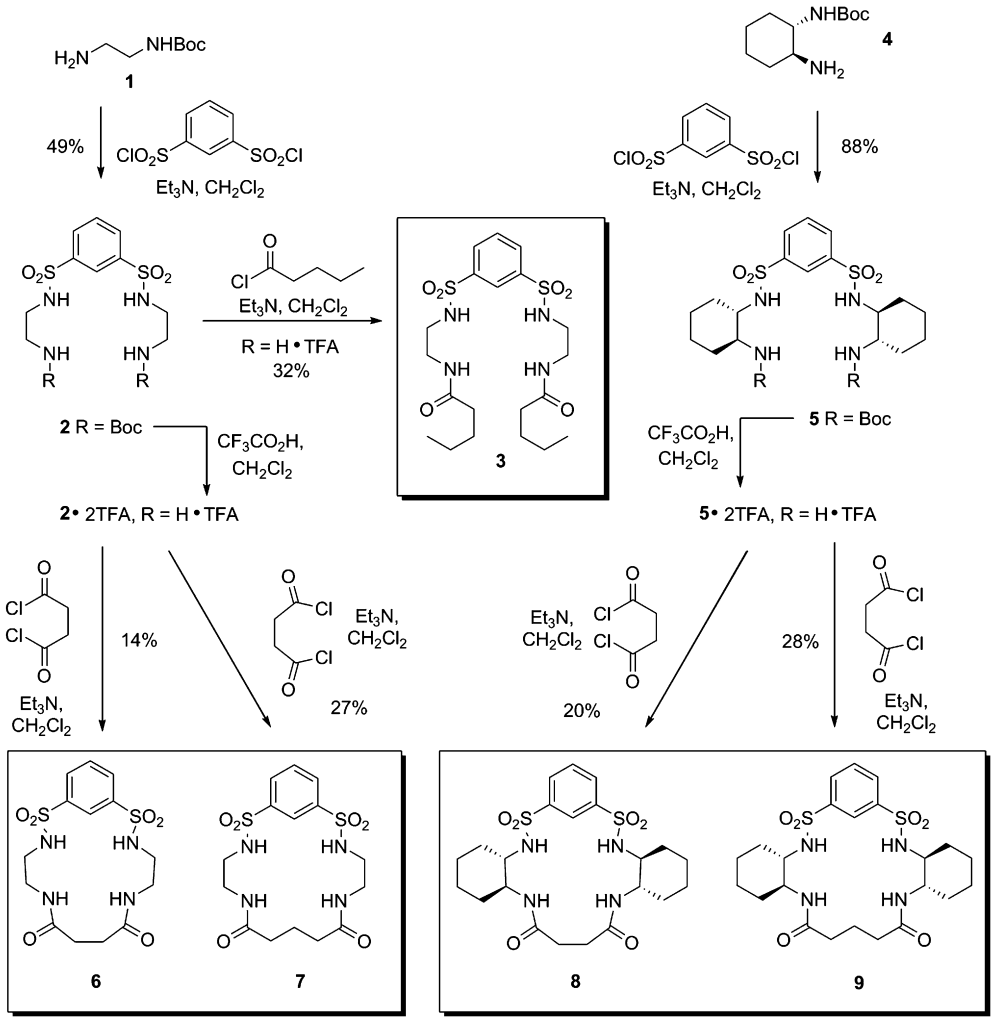


Figure 1. Schematic representation of acetate binding by (a) Crabtree's benzene-1,3-disulfonamide, and proposed (b) acyclic and (c,d) macrocyclic benzene-1,3-disulfonamide receptor scaffolds.

receptors. Furthermore, the size of the binding cavity was varied with both achiral (**6**, **7**) and chiral (**8**, **9**) analogues (Scheme 1).

Ethylene diamine was mono-Boc protected[14] to give **1**, which was coupled with benzene-1,3-disulfonyl chloride, furnishing **2**. Removal of the Boc protecting groups and coupling with 2 equiv of valeryl chloride provided acyclic receptor **3** in a modest unoptimised yield. A [1+1] direct macrocyclisation between diamine **2**·2TFA salt and succinyl- or glutaryl- diacid chlorides, under high dilution conditions, afforded achiral macrocycles **6** and **7**, respectively. Both **6** and **7** were obtained in modest yield, although the former in somewhat lower yield presumably as a result of increased conformational strain in the [1+1] macrocyclisation which may favour formation of the undesired [2+2] cyclisation product.[15]

Chiral bis-amine derived receptors **8** and **9** were prepared in analogous fashion. *N*-Boc-(*S*,*S*)-cyclohexane-1,2-diamine **4** was prepared via mono-Boc protection of (1*S*,2*S*)-(−)-1,2-diaminocyclohexane D-tartrate and coupled with benzene-1,3-sulfonyl chloride, furnishing **5** in good yield. Once again, deprotection of **5** and subsequent [1+1] coupling, with both succinyl- and glutaryl-chloride, of the bis-amine liberated from **5**·2TFA salt under basic, high dilution conditions, afforded macrocyclic products **8** and **9**, respectively; the chiral analogues of **6** and **7**. Macrocycles **6** and **7** were soluble only in hygroscopic dimethylsulfoxide (DMSO) and we were unable to obtain diffraction grade single crystals. However, (*S*,*S*)-cyclohexane-1,2-diamine-derived receptor **8** was crystallised by vapour diffusion from MeOH. The crystal structure is



Scheme 1. Synthesis of bis-amine derived, benzene-1,3-disulfonamide receptors.

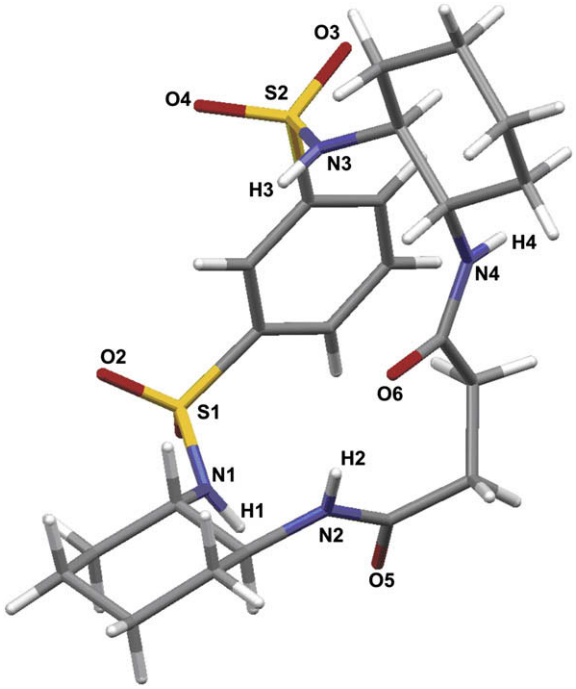


Figure 2. X-ray crystal structure of **8** illustrating antiparallel array of (*S,S*)-1,2-cyclohexyl-linked amide and sulfonamide H-bond donors, solvent excluded, partial numbering for clarity.

characterised by intramolecular hydrogen bonding, importantly between N1–H1···O5 [N1···O5 2.971(7) Å] and between N2–H2···O6 [N2···O6 2.777(6) Å] (Fig. 2). The observed conformation results in antiparallel positioning of sulfonamide and amide hydrogen bond donors around the macrocycle and suggests that substantial reorganisation would be required to align all four hydrogen bond donors with an anionic guest. Unfortunately we did not succeed in crystallising the homologous macrocycle **9**.

Table 1
Anion templating effect upon [1+1] condensation between **11** and 1,5-diaminopntane[a]

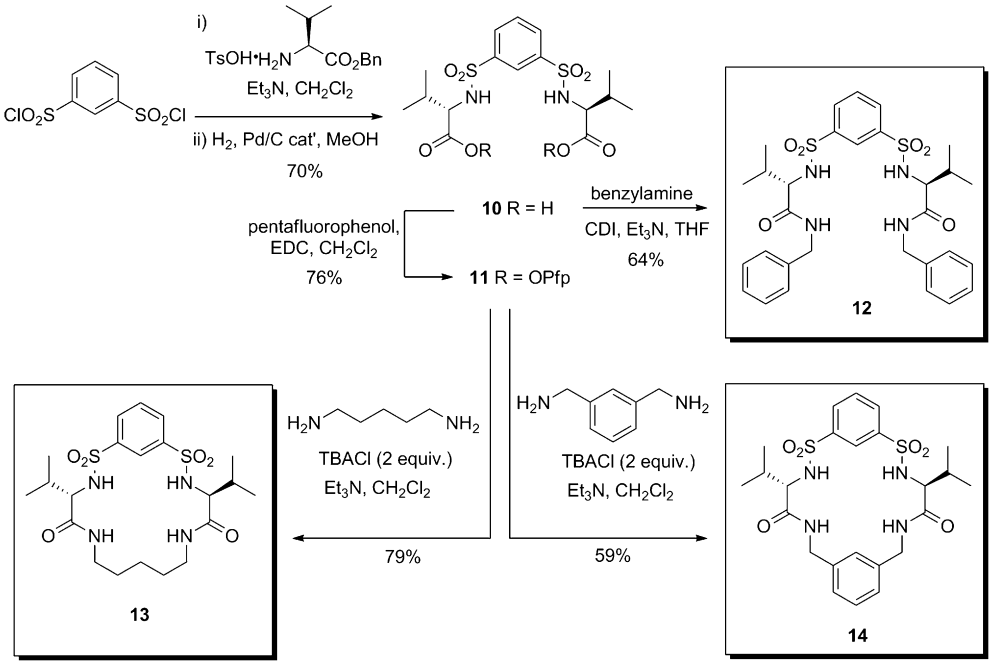
Entry	Templating anion	Yield [%] of **13**[b]
1	None	28[c]
2	Cl^-	79
3	Br^-	65
4	$H_2PO_4^-$	0
5	AcO^-	21

[a] Typically, 4 mL aliquots of each of a 0.07 M solution of **11** in CH_2Cl_2 containing 2 equiv TBA salt, and a 0.07 M solution of 1,5-diaminopentane in CH_2Cl_2 containing 3.4 equiv Et_3N were added into CH_2Cl_2 (20 mL) over 1.75 h.
[b] Yields refer to isolated, analytically pure material purified by column chromatography.
[c] [2+2] Cyclisation product was also isolated in 26% yield.

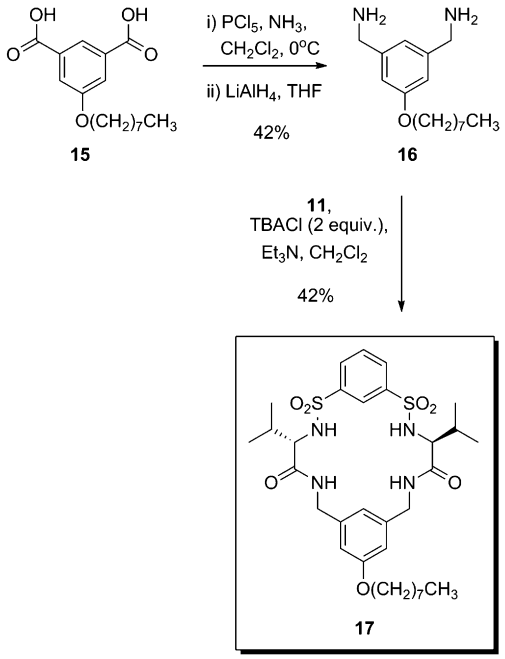
Synthesis of L-valine derived receptors relied upon [1+1] cyclisation of an activated bis-carboxylic ester **11** with a diamine coupling partner as the key step.

Assembly of the cyclisation precursor **11** was made in three steps; the bis-sulfonamide scaffold was constructed upon coupling of benzene-1,3-disulfonyl chloride with 2 equiv of L-valine benzyl ester, catalytic hydrogenolysis then furnished diacid **10** and conversion to bis-pentafluorophenyl (Pfp) ester **11** was straightforward (Scheme 2). Preparation of an acyclic receptor **12** was accomplished in reasonable yield, using a carbonyldiimidazole (CDI) mediated coupling of diacid **10** and benzylamine. Attempted CDI-mediated cyclisation of diacid **10**, both with 1,5-diaminopentane and *m*-xylylenediamine, gave rise to unwanted [2+2] cyclisation products, and [1+1] cyclisation products **13** and **14** were obtained in yields of only 23% and 6%, respectively. Several reports of anion templated macrocyclisation have been made recently[16] and we also attempted anion templated synthesis of macrocycles **13** and **14**.

Condensation of **11** with 1,5-diaminopentane was conducted in the presence of tetra-*n*-butylammonium (TBA) salts of Cl^-, Br^-, $H_2PO_4^-$ and AcO^- (Table 1). Templation by Cl^- and Br^- is evidenced by substantial improvement in the yield of [1+1] product **13**,



Scheme 2. Synthesis of L-valine derived benzene-1,3-disulfonamide receptors.



Scheme 3. Synthesis of L-valine derived benzene-1,3-disulfonamide receptor.

without formation of the [2+2] product in the presence of either anion (entries 1–3). No reaction occurred in the presence of n-$Bu_4N^+H_2PO_4^-$ (entry 4) and AcO^- failed to influence the macrocyclisation; in the presence of AcO^-, **13** was obtained in similar yield to that observed under non-templated CDI-mediated coupling conditions (entry 5). This suggests that the receptor motif may demonstrate closer fit of the macrocyclic cavity and preferred binding to Cl^- and Br^- anion guests than to carboxylate in non-polar organic solvents.

The TBACl templated macrocyclisation conditions were used for the preparation of **14**, in good yield (Scheme 2).

Finally, preparation of L-valine derived receptor **17**, directly analogous in structure with **14** but bearing solublising alkyl functionality, was carried out, once again via macrocyclisation of activated bis-Pfp ester **11** with a bis-amine coupling partner **16** (Scheme 3). 5-Octyloxy-isophthalic acid (**15**) was obtained from dimethyl-5-hydroxyisophthalate following alkylation and saponification.[17] Amidation and reduction steps furnished **16** and TBACl templated coupling of **16** with **11** gave the anticipated macrocyclic product **17**.

X-ray crystal structures of macrocycles **13** and **14** indicate that the directionality of hydrogen bond donor groups alternates around the receptor cavity in both cases (Fig. 3).

2.2. Binding studies

The binding properties of all of the disulfonamide derived receptors were investigated using the tetra-n-butylammonium salts of various anions and in various solvents using standard NMR titration experiments.[18] Initial studies were carried out with the acyclic disulfonamides **2** and **3**, which were not soluble in $CDCl_3$ and titration experiments with n-$Bu_4N^+AcO^-$ were therefore carried out using MeCN-d_3 as solvent. For both **2** and **3** the sulfonamide NH resonance broadened on addition of the acetate guest, but a downfield shift of the amide resonance was observed (**2**: $\Delta\delta_{max}$ >1.20 ppm, **3**: $\Delta\delta_{max}$ >2.16 ppm) consistent with the formation of hydrogen bonds. The titration curves did not reach saturation (4.77 equiv and 6.25 equiv added guest to **2** and **3**, respectively) and the data could not be fitted to a simple 1:1 (host–guest) binding isotherm but instead to a 1:2 (host–guest) binding isotherm in which binding is dominated by a large 1:1 (H+G) association (**2**: $K_a^{1:1}$ 3.6×10^4 M^{-1}, **3**: $K_a^{1:1}$ 1.1×10^4 M^{-1}) with only a very small contribution from sequential 1:2 (HG+G) binding (Table 2, entries 1, 2). Dominant 1:1 stoichiometry for binding of acetate by receptor **2** was confirmed by Job plot.[19] The ^1H NMR spectra of **2** and **3** also showed an initial downfield shift of the aromatic C^2–H proton upon addition of up to 1 equiv AcO^- followed by an upfield shift with further equivalents of added guest (Fig. 4).

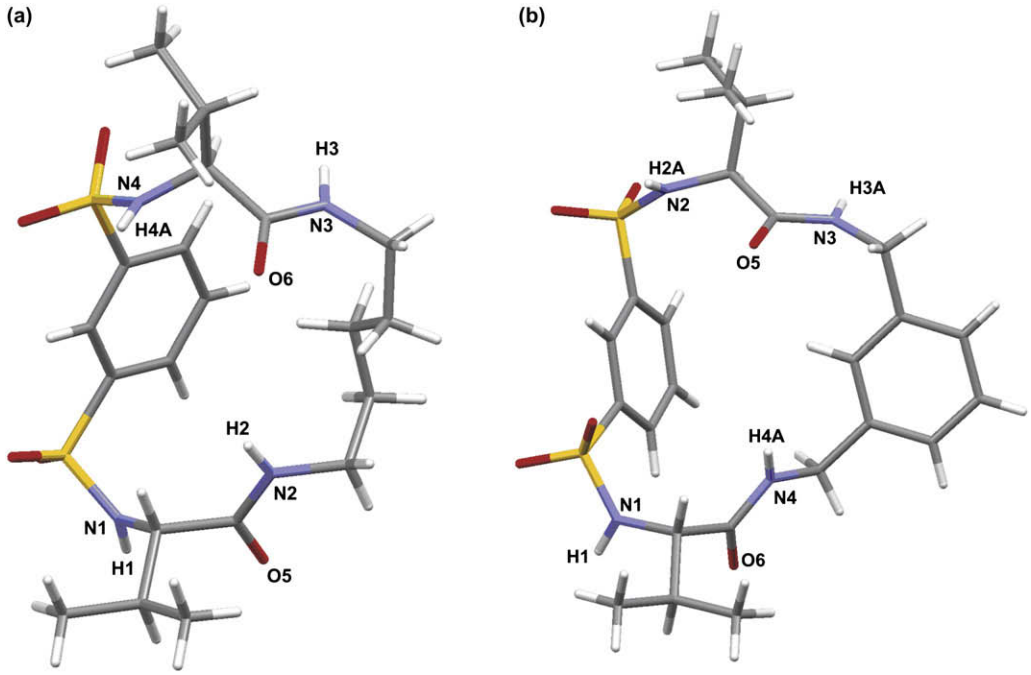


Figure 3. (a) X-ray crystal structures of (a) **13** and (b) **14**, illustrating antiparallel arrays of (*S*,*S*)-1,2-cyclohexyl-linked amide and sulfonamide H-bond donors, solvent excluded, partial numbering for clarity.

Table 2
^{1}H NMR titration data for binding of disulfonamide receptors **2**, **3**, **6**–**9** and **12**–**14** with tetra-*n*-butylammonium acetate in various solvents at 298 K

Entry	Receptor	Solvent	Stoichiometry of binding	K_a (M^{-1}) [%error[a]]	ΔG (kJ/mol)
1	**2**	MeCN-d_3	1:1+1:2	$K_a^{1:1}$=36,000 [<5] $K_a^{1:2}$=26 [<5]	−26.0
2	**3**	MeCN-d_3	1:1+1:2	$K_a^{1:1}$=11,000 [<5] $K_a^{1:2}$=4 [<5]	−23.0
3	**12**	MeCN-d_3	1:1+1:2	$K_a^{1:1}$=3640 [<5] $K_a^{1:2}$=32 [<5]	−20.3
4	**8**	MeCN-d_3	1:1	$K_a^{1:1}$=989 [11]	−17.1
5	**9**	MeCN-d_3	1:1	$K_a^{1:1}$=1830 [6]	−18.6
6	**13**	MeCN-d_3	1:1	$K_a^{1:1}$=>10^4	—
7	**14**	MeCN-d_3	1:1	$K_a^{1:1}$=>10^4	—
8	**6**	DMSO-d_6	1:1	$K_a^{1:1}$=236 [<5]	−13.5
9	**7**	DMSO-d_6	1:1+1:2	$K_a^{1:1}$=710 [8] $K_a^{1:2}$=8 [8]	−16.3
10	**8**	$CDCl_3$	1:1+1:2	—[b]	—
11	**9**	$CDCl_3$	1:1	$K_a^{1:1}$=758 [9]	−16.4

[a] When more than one proton could be monitored during the same titration the error was calculated on the basis of the average of all constants calculated. When only one proton could be monitored the reported errors were calculated with EQNMR software,[22] errors calculated below the 5% threshold in EQNMR are reported as <5%.
[b] Data were not fitted reliably.

This can be attributed to tight binding of a first equivalent of acetate by both sulfonamides simultaneously, followed by binding of a second acetate by the two sulfonamides separately, as has been proposed by Crabtree et al.[10g] for binding of acetate or fluoride by simple acyclic disulfonamide receptors, and by others[10d] (Scheme 4). Notably the C^2–H proton is significantly affected in the 1:1 binding mode, accounting for its pronounced downfield shift on addition of the first equivalent of acetate, but is relatively unaffected in the 1:2 binding mode, accounting for the subsequent upfield shift back towards its unperturbed position as more acetate is added. The acyclic disulfonamide **12** behaved very similarly to the acyclic receptors **2** and **3** on addition of acetate (Table 2, entry 3). Hence the amide NH resonance shifted downfield in the titration experiment ($\Delta\delta_{max}$ >2.30 ppm) and gave a good fit to a sequential 1:2 binding isotherm, which is dominated by 1:1 association ($K_a^{1:1}$ 3.6×10^3 M^{-1}) with a much smaller 1:2 association ($K_a^{1:2}$ 32 M^{-1}). Similarly an initial downfield shift of the aromatic C^2–H proton of **12** upon addition of up to 1 equiv AcO^- ($\Delta\delta_{max}$=0.27 ppm) is observed, followed by an upfield shift with addition of further guest.

We wished to compare the binding properties of macrocyclic receptors with the analogous acyclic receptors, but unfortunately both **6** and **7** were insoluble in MeCN-d_3. However, titration of **8** and **9** with *n*-$Bu_4N^+AcO^-$ in MeCN-d_3 again led to broadening of sulfonamide protons in the ^{1}H NMR spectrum, but also a defined downfield shift of amide NH resonances (**8**: $\Delta\delta_{max}$=1.42 ppm, **9**: $\Delta\delta_{max}$=1.43 ppm), which could be fitted to 1:1 binding isotherm (**8**: $K_a^{1:1}$ 989 M^{-1}, **9**: $K_a^{1:1}$ 1830 M^{-1}) (Fig. 5 and Table 2, entries 4, 5). No evidence for 1:2 complexation was observed in either case. Hence, the 1:2 complex formation observed in the acyclic series is suppressed, but the constraint of the macrocyclic framework is counterproductive. The more flexible macrocycle **9** binds acetate guest in MeCN-d_3 more tightly than does receptor **8** but binding in both cases is significantly weaker than was observed for the acyclic analogues **2** and **3**. However, in contrast to receptors **8** and **9**, constraining the L-valine derived disulfonamides into macrocycles **13** and **14** proved advantageous. Hence **13** and **14** demonstrated high affinity for AcO^- in MeCN-d_3. Titration curves obtained by monitoring the amide NH resonance gave in each case a linear increase in δ_H with increasing [AcO^-] and a sharp plateau after addition of 1 equiv guest anion. The data implies very tight 1:1 binding (Table 2, entries 6, 7) but is beyond the upper limit (K_a >10^4 M^{-1}) of association constants that can be accurately determined by NMR titration.[20]

For macrocycles **6** and **7** we were only able to carry out titrations with *n*-$Bu_4N^+AcO^-$ using DMSO-d_6 as solvent (Table 2, entries 8, 9) and unsurprisingly, association constants were found to be lower in this solvent. Downfield shift of the amide NH resonance of receptor **6** gave a straightforward titration curve, which gave a good fit with a 1:1 binding isotherm, but a low association constant ($K_a^{1:1}$ 239 M^{-1}). Addition of acetate also led to a downfield shift of the receptor **6** C^2–H aromatic proton. For homologous receptor **7**, on the other hand, the titration curve for the C^2–H proton initially shifts downfield and then reverses upfield following addition of more than 2 equiv of AcO^- (Fig. 6). Close fit to a 1:1 binding isotherm could not be made for the titration curves. Titration of **7** with AcO^- also results in downfield shift of the amide NH resonance, and fit of the data to a sequential 1:2 (HG+G) binding isotherm confirmed contribution of a partial 1:2 binding ($K_a^{1:2}$ 8 M^{-1}) association, although 1:1 stoichiometry dominates ($K_a^{1:1}$ 710 M^{-1}).

Receptors **8** and **9**, on the other hand, also proved to be soluble in $CDCl_3$. Titration of **8** with *n*-$Bu_4N^+AcO^-$ in $CDCl_3$ (Table 2, entry 10) resulted in downfield shift of the amide NH resonance, indicating involvement of the amide functionality in hydrogen bonding, but a relatively small change in shift of the sulfonamide NH resonance ($\Delta\delta_{max}$=0.36 ppm) suggesting that these protons are less accessible for binding. However, the titration curves could not be reliably fitted to a 1:1 or a 1:2 binding isotherm,[21] which suggests that multiple receptor-

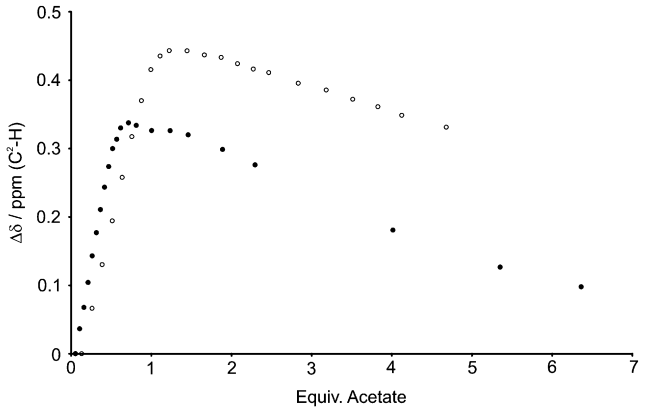
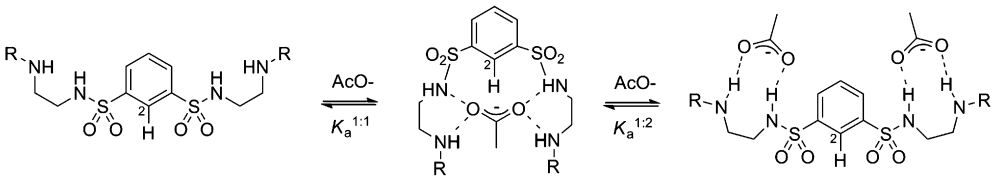


Figure 4. Binding titration curves of acyclic receptors (○) **2** and (●) **3** with tetra-*n*-butylammonium acetate in MeCN-d_3, showing the shift of the aromatic C^2–H proton.



2 R = Boc
3 R = $(CH_2)_3CH_3$

(**2**/**3**) • AcO^-

(**2**/**3**) • $2AcO^-$

Scheme 4. Proposed formation of 1:1 (**2**/**3**)·AcO^- and 1:2 (**2**/**3**)·$2AcO^-$ complexes.

anion equilibria are present in $CDCl_3$. For macrocycle **9** the titration curve obtained, monitoring the amide NH resonance on addition of AcO^- in $CDCl_3$ ($\Delta\delta_{max}$ >2.10 ppm), gave a reasonable fit using a 1:1 binding isotherm (Table 2, entry 11). However, a low binding constant for this association ($K_a^{1:1}$ 758 M^{-1}) and negligible change in shift of the aromatic C^2–H proton following addition of guest ($\Delta\delta_{max}$ ~0.05 ppm) indicates that the guest anion is not accommodated within the macrocyclic cavity by multiple hydrogen-bonded interactions but is most likely bound externally.

The L-valine derived receptors **13** and **14** both proved to be potent receptors for acetate in MeCN-d_3 solvent, whereas **6**–**9** were relatively poor receptors, and indeed were weaker than their acyclic analogues. Receptors **13** and **14** were therefore selected for further binding studies with other anions. These studies were carried out using a more competitive solvent mixture, MeCN-d_3/2% H_2O as binding of acetate in neat MeCN-d_3 had proven to be beyond the limit of accurate determination by NMR titration experiments. In MeCN-d_3/2% H_2O the titration of **13** and **14** with acetate, monitoring the chemical shift of the amide NH proton, gave clean 1:1 binding (**13**: $K_a^{1:1}$ 540 M^{-1}, **14**: $K_a^{1:1}$ 351 M^{-1}). Receptor **14** proved to be only sparingly soluble in this solvent mixture however, whereas the analogous receptor **17** was much more soluble, gave an essentially identical binding result with acetate (**17**: $K_a^{1:1}$ 372 M^{-1}) and was therefore used in subsequent studies. Titrations, using receptors **13** and **17**, were carried out using the tetra-*n*-butylammonium salts of acetate, dihydrogen phosphate, chloride and bromide and all gave reliable data with good fit to a 1:1 binding isotherm (Table 3). Titration curves indicating the chemical shift of the amide NH proton of each macrocycle with each of these anions are shown in Figure 7.

Both receptors **13** and **17** demonstrate a preference for binding oxyanions over halides, according to the trend $AcO^- > H_2PO_4^- > Cl^- > Br^-$, in reversal of the templating effect of these anions in macrocycle synthesis under less polar conditions. The more flexible receptor, **13** is a slightly stronger receptor than **17** for each anion. In a final series of titration experiments, the binding of macrocycle **17** with the four anions was measured in MeCN-d_3/1% H_2O (Table 3, entries 10–13), which unsurprisingly gave higher association constants than in MeCN-d_3/2% H_2O, but also showed greater selectivity between the four anions.

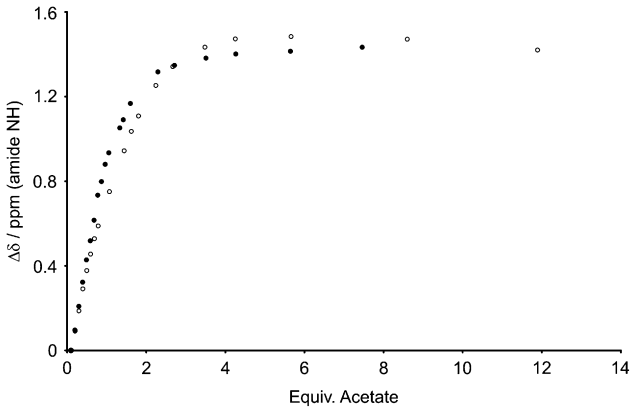


Figure 5. Binding titration curves of macrocycles (○) **8** and (●) **9** with tetra-*n*-butylammonium acetate in MeCN-d_3, showing the shift of the amide NH resonance.

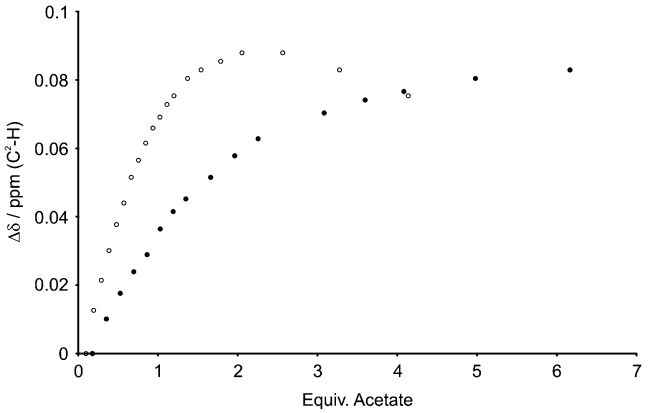


Figure 6. Binding titration curves of macrocycles (●) **6** and (○) **7** with tetra-*n*-butylammonium acetate in DMSO-d_6, showing the shift of the aromatic C^2–H proton.

Table 3
^{1}H NMR titration data for binding of L-valine derived disulfonamide receptors with various anions at 298 K

Entry	Receptor	Anion[a]	Solvent	$K_a^{1:1}$ (M^{-1}) [%error[b]]	ΔG (kJ/mol)
1	**14**	AcO^-	MeCN-d_3/2% H_2O	351 [<5%]	−14.5
2	**13**	AcO^-	MeCN-d_3/2% H_2O	540 [<5%]	−15.6
3	**13**	$H_2PO_4^-$	MeCN-d_3/2% H_2O	281 [<5%]	−14.0
4	**13**	Cl^-	MeCN-d_3/2% H_2O	183 [<5%]	−12.9
5	**13**	Br^-	MeCN-d_3/2% H_2O	111 [<5%]	−11.7
6	**17**	AcO^-	MeCN-d_3/2% H_2O	372 [<5%]	−14.7
7	**17**	$H_2PO_4^-$	MeCN-d_3/2% H_2O	201 [<5%]	−13.1
8	**17**	Cl^-	MeCN-d_3/2% H_2O	104 [c]	−11.5
9	**17**	Br^-	MeCN-d_3/2% H_2O	55 [c]	−9.9
10	**17**	AcO^-	MeCN-d_3/1% H_2O	2690 [<5%]	−19.6
11	**17**	$H_2PO_4^-$	MeCN-d_3/1% H_2O	866[<5%]	−16.7
12	**17**	Cl^-	MeCN-d_3/1% H_2O	328 [11%]	−14.3
13	**17**	Br^-	MeCN-d_3/1% H_2O	134 [13%]	−12.1

[a] Anions were added as tetra-*n*-butylammonium salts.
[b] When more than one proton could be monitored during the same titration the error was calculated on the basis of the average of all constants calculated. When only one proton could be monitored the reported errors were calculated with EQNMR software,[22] errors calculated below the 5% threshold in EQNMR are reported as <5%.
[c] Due to a low percentage saturation of the receptor, association constants should be considered of approximate magnitude.

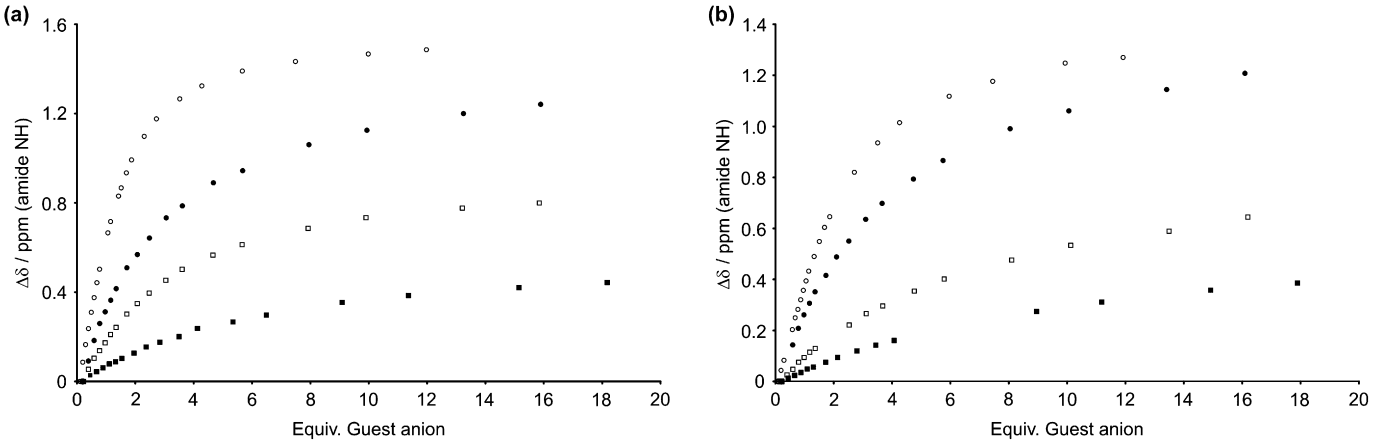


Figure 7. Binding titration curves of (a) macrocycle **13** and (b) macrocycle **17** with tetra-*n*-butylammonium salts of AcO^- (○), H_2PO_4 (●), Cl^- (□) and Br^- (■) in MeCN-d_3/2% H_2O, showing the shift of the amide NH resonance.

3. Conclusion

We have prepared a series of acyclic and macrocyclic disulfonamide receptors. Synthesis of these compounds, from benzene-1,3-disulfonyl chloride was straightforward. The synthesis of the macrocyclic compounds benefited from a substantial templating effect using chloride and bromide ions, but not using acetate or phosphate. The acyclic disulfonamides proved to be potent receptors for carboxylates in MeCN-d_3 although, as has been observed previously with simpler disulfonamide receptors, binding involves both 1:1 and 1:2 binding stoichiometries.

Macrocyclisation of the basic acyclic receptor structure served to suppress the 1:2 binding mode such that the macrocyclic receptors generally showed clean 1:1 binding. However, macrocycles **8** and **9** proved to be weaker binders of carboxylate than their acyclic analogues whereas macrocycles **13** and **14** were significantly stronger. The crystal structure of macrocycle **8** indicates a conformation, stabilised by at least one intramolecular hydrogen bond, with alternating NHs pointing in opposite directions as one moves around the macrocyclic ring, rather than convergent on one face of the macrocycle as would be preferred for strong anion recognition. Crystal structures of macrocycles **13** and **14** on the other hand, also indicate alternate NHs to be pointing in opposite directions; but both of these macrocycles appear to be more flexible and lack intramolecular hydrogen bond stabilisation of the conformation, possibly explaining the much greater anion-binding affinity of **13** and **14**, but rather limited selectivity between anions. Work towards application of amino acid-derived disulfonamide receptor macrocycles for enantioselective carboxylate recognition is in progress.

4. Experimental

4.1. General techniques

Unless otherwise stated, reagents and solvents were obtained from commercial suppliers and if necessary dried and distilled before use. THF was freshly distilled from sodium benzophenone ketal under argon. Dichloromethane, acetonitrile and triethylamine were freshly distilled from CaH_2 as was petroleum ether where the fraction boiling between 40 and 60 °C was used. Reactions requiring a dry atmosphere were conducted in oven dried glassware under nitrogen. Column chromatography was performed on Sorbsil C60, 40–60 mesh silica.

^1H and ^{13}C NMR spectra were recorded on Bruker AV300, AM300 or DPX400 spectrometers. ^1H chemical shifts are reported as values in parts per million referenced to residual solvent. The following abbreviations are used to denote multiplicity and may be compounded: s=singlet, d=doublet, t=triplet, q=quartet, fs=fine splitting. Broadened resonances are abbreviated: br. Coupling constants, *J*, are measured in hertz (Hz). ^{13}C spectra were proton decoupled and referenced to solvent. The number of adjacent protons was determined by DEPT experiments.

Infra-red spectra were recorded on a BIORAD Golden Gate FTS 135. All samples were run either as neat solids or as oils. Absorptions are given in wavenumbers (cm^{-1}) and the following abbreviations used to denote peak intensities: s=strong, m=medium, w=weak and/or br (broad).

Low resolution mass spectra were recorded on a Micromass Platform II single quadrupole mass spectrometer in methanol or acetonitrile. Accurate mass spectra were recorded on a VG analytical 70-250-SE double focussing mass spectrometer.

Melting points were determined in open capillary tubes using a Gallenkamp Electrothermal melting point apparatus and are uncorrected. Optical rotations were measured on a PolAr2001 polarimeter using the solvent stated, the concentration given is in g/100 mL.

Microanalyses were performed by MEDAC Ltd., Surrey.

4.2. ^1H NMR titration experiments[18]

^1H NMR titration experiments were conducted on a Brüker AM300 spectrometer at 298 K. Deuterated solvents of commercial grade were used. Inorganic guests, TBA acetate, dihydrogen phosphate, fluoride, chloride and bromide were of commercial grade. The correct stoichiometry was verified performing NMR experiments with long scan delays. A sample of host was dissolved in the deuterated solvent or solvent mixture. A portion of this solution was used as the host NMR sample and the remainder used to dissolve a sample of the guest, so that the concentration of the host remained constant throughout the titration. Guest stock solutions were typically prepared such that 10 μL of that solution contained 0.1 equiv of guest with respect to host, unless otherwise stated. Successive aliquots of the guest solution were added to the host NMR sample and ^1H NMR sample recorded after each addition. Changes in chemical shift of host proton signals, as a function of guest concentration, were analysed using NMRTit HG and NMRTit HGG software, assuming a 1:1 or 1:2 binding stoichiometry. When more than one proton could be monitored during the same titration

the error was calculated on the basis of the average of all constants calculated. When only one proton could be monitored the reported errors were calculated with EQNMR software,[22] errors calculated below the 5% threshold in EQNMR are reported as <5%.

4.3. Synthetic procedures

Preparation of 1-(*tert*-butyloxycarbonyl)ethyldiamine (**1**) according to the method of Anslyn[23] has been reported previously.[14] *N*-Benzyloxycarbonyl-(*S*,*S*)-cyclohexane-1,2-diamine (**4**) was prepared from (1*S*,2*S*)-(−)-1,2-diaminocyclohexane D-tartrate and has been reported previously.[24]

*4.3.1. {2-[3-(2-tert-Butoxycarbonylamino-ethylsulfamoyl)-benzenesulfonylamino]-ethyl}-carbamic acid tert-butyl ester (**2**)*

A solution of benzene-1,3-disulfonyl chloride (4.75 g, 17.3 mmol) in CH_2Cl_2 (30 mL) was added dropwise to a stirred solution of 1-(*tert*-butyloxycarbonyl)ethyldiamine **1** (6.08 g, 38.0 mmol) and Et_3N (2.5 mL, 17.9 mmol) in CH_2Cl_2 (80 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight under N_2 before dilution with CH_2Cl_2 (100 mL), washing with $KHSO_4$ (100 mL of a 1 M aqueous solution), K_2CO_3 (100 mL of a 1 M aqueous solution) and brine (100 mL), drying over $MgSO_4$ and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with 1:1 petroleum ether/EtOAc) gave the title compound **2** as a white solid (4.42 g, 49%). Mp 64–66 °C; IR (neat): ν_{max}=3273 (w), 2980 (w), 2935 (w), 1682 (s), 1516 (m), 1331 (s), 1153 (s), 1083 (s), 793 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.34 (1H, s), 8.06 (2H, dd, *J*=8.0, 2.0 Hz), 7.67 (1H, t, *J*=8.0 Hz), 5.61 (2H, br s), 4.91 (2H, br s), 3.22 (4H, q, *J*=5.5 Hz), 3.12 (4H, q, *J*=5.5 Hz), 1.43 (18H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.8, 141.8, 130.9, 130.2, 125.5, 80.2, 43.9, 40.4, 28.5; ESMS: (*m*/*z*) 545 $[M+Na]^+$; HRMS (ES): calcd for $C_{20}H_{35}N_4O_8S_2$ ($[M+H]^+$) 523.1896, found 523.1892; calcd for $C_{20}H_{34}N_4NaO_8S_2$ ($[M+Na]^+$) 545.1710, found 545.1709.

*4.3.2. (**2**)·2TFA salt*

A solution of bis-sulfonamide **2** (1.95 g, 3.73 mmol) in 4:1 CH_2Cl_2/TFA (50 mL) was stirred for 5 h at room temperature. Toluene was added and the solvent was removed under reduced pressure. Trituration of the oily residue obtained with MeCN gave the title compound as a white solid, collected by filtration (1.69 g, 82%). Mp 200–204 °C; IR (neat): ν_{max} 3161 (w), 1668 (s), 1595 (w), 1342 (m), 1191 (m), 1138 (s), 1079 (m), 798 (s) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 8.40–8.10 (2H, br s), 8.20 (1H, t, *J*=2.0 Hz), 8.10 (2H, dd, *J*=8.0, 2.0 Hz), 8.00 (6H, br s), 7.90 (1H, t, *J*=8.0 Hz), 3.01 (4H, t, *J*=6.0 Hz), 2.89 (4H, t, *J*=6.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 158.5 (q, *J*=31 Hz), 140.9, 131.1, 130.6, 124.6, 117.1 (q, *J*=300 Hz), 40.0, 38.6.

*4.3.3. Pentanoic acid {2-[3-(2-pentanoylamino-ethylsulfamoyl)-benzenesulfonylamino]-ethyl}-amide (**3**)*

Valeryl chloride (80 μL, 0.675 mmol) was added dropwise to a solution of (**2**)·2TFA salt (175 mg, 0.318 mmol) and Et_3N (200 μL, 1.43 mmol) in MeCN (10 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight under N_2. Solvent was then removed in vacuo and the residue obtained was dissolved in CH_2Cl_2 (50 mL) and washed with $KHSO_4$, (50 mL of a 1 M aqueous solution), K_2CO_3 (50 mL of a 1 M aqueous solution) and brine (500 mL) before drying over $MgSO_4$ and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with CH_2Cl_2→96:4 CH_2Cl_2/MeOH) gave the title compound **3** as a white solid (50 mg, 32%). Mp 64–66 °C; IR (neat): ν_{max} 3606 (w), 3254 (w), 2956 (w), 2931 (w), 2871 (w), 1630 (s), 1558 (s), 1431 (m), 1317 (s), 1147 (s), 1082 (s), 1073 (s), 796 (m) cm^{-1}; ^1H NMR (400 MHz, MeCN-d_3): δ 8.21 (1H, t, *J*=2.0 Hz), 8.03 (2H, dd, *J*=8.0, 2.0 Hz), 7.76 (1H, t, *J*=8.0 Hz), 6.57 (2H, br s), 6.26 (2H, br s), 3.15 (4H, q, *J*=6.0 Hz), 2.96 (4H, q, *J*=6.0 Hz), 2.06 (4H, t, *J*=7.5 Hz), 1.53–1.44 (4H, m), 1.28 (4H, sext, *J*=7.0 Hz), 0.88 (6H, t); ^{13}C NMR (100 MHz, MeCN-d_3): δ 175.0, 142.5, 131.6, 131.5, 126.1, 44.1, 39.6, 36.5, 28.5, 23.0, 14.1; ESMS: (*m*/*z*) 513 $[M+Na]^+$; HRMS (ES): calcd for $C_{20}H_{35}N_4O_6S_2$ ($[M+H]^+$) 491.1993, found 491.1988.

*4.3.4. Macrocycle **6***

A solution of (**2**)·2TFA salt (201 mg, 0.365 mmol) and Et_3N (255 μL, 1.83 mmol) in MeCN (4 mL), and a solution of succinyl dichloride (41 μL, 0.372 mmol) in MeCN (4 mL) were added simultaneously, via syringe pump, into a flask equipped with condensor and $CaCl_2$ drying tube containing MeCN (60 mL) at 60 °C over 4 h. The resultant mixture was stirred overnight at 60 °C before cooling and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with CH_2Cl_2→94:6 CH_2Cl_2/MeOH) and subsequent washing with MeOH gave the title compound **6** as a white solid (21 mg, 14%). Mp >240 °C (decomposes); IR (neat): ν_{max} 3301 (s), 3090 (w), 1650 (s), 1547 (s), 1434 (m), 1335 (s), 1177 (s), 1154 (s), 1106 (m), 1074 (m), 867 (m), 795 (m) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.11 (1H, t, *J*=1.5 Hz), 8.04 (2H, dd, *J*=8.0, 1.5 Hz), 7.91 (1H, t, *J*=8.0 Hz), 7.87 (2H, t, *J*=6.0 Hz), 7.72 (2H, br s), 3.06–2.97 (4H, m), 2.64 (4H, t, *J*=7.5 Hz), 2.22 (4H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 140.2, 131.4, 130.4, 125.1, 41.9, 38.0, 31.2; ESMS: (*m*/*z*) 405 $[M+H]^+$; HRMS (ES): calcd for $C_{14}H_{21}N_4O_6S_2$ ($[M+H]^+$) 405.0897, found 405.0902; calcd for $C_{14}H_{20}N_4NaO_6S_2$ ($[M+Na]^+$) 427.0716, found 427.0719.

*4.3.5. Macrocycle **7***

A solution of (**2**)·2TFA salt (220 mg, 0.401 mmol) and Et_3N (280 μL, 2.01 mmol) in MeCN (4 mL), and a solution of glutaryl dichloride (52 μL, 0.407 mmol) in MeCN (4 mL) were added simultaneously, via syringe pump, into a flask equipped with condensor and $CaCl_2$ drying tube containing MeCN (70 mL) at 60 °C over 4 h. The resultant mixture was stirred overnight at 60 °C before cooling and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with CH_2Cl_2→92.5:7.5 CH_2Cl_2/MeOH) and subsequent washing with MeOH, gave the title compound **7** as a white solid (46 mg, 27%). Mp >240 °C (decomposes); IR (neat): ν_{max} 3275 (s), 3087 (w), 2953 (w), 2874 (w), 1640 (s), 1543 (s), 1447 (m), 1331 (s), 1148 (s), 1086 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 8.21 (1H, t, *J*=2.0 Hz), 8.04 (2H, dd, *J*=8.0, 2.0 Hz), 7.87 (1H, t, *J*=8.0 Hz), 7.75 (2H, t, *J*=6.0 Hz), 7.68 (2H, t, *J*=6.0 Hz), 3.00 (4H, dt, *J*=6.0, 7.0 Hz), 2.77 (4H, dt, *J*=6.0, 7.0 Hz), 1.97 (4H, t, *J*=6.5 Hz), 1.67 (2H, quin, *J*=6.5 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 140.9, 131.0, 130.3, 125.0, 42.2, 37.7, 34.0, 20.0; ESMS: (*m*/*z*)=419 $[M+H]^+$; HRMS (ES): calcd for $C_{15}H_{22}N_4NaO_6S_2$ ($[M+Na]^+$) 441.0873, found 441.0866.

*4.3.6. 1,3-Bis-((1S,2S)-2-tert-butoxycarbonylamino cyclohexylsulfamoyl)-benzene (**5**)*

A solution of benzene-1,3-disulfonyl chloride (915 mg, 3.32 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a stirred solution of *N*-benzyloxycarbonyl-(*S*,*S*)-cyclohexane-1,2-diamine **4** (1.44 g, 6.73 mmol) and Et_3N (950 μL, 6.82 mmol) in CH_2Cl_2 (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight under N_2 before dilution with CH_2Cl_2 (90 mL), washing with $KHSO_4$ (80 mL of a 1 M aqueous solution), K_2CO_3 (80 mL of a 1 M aqueous solution) and brine (80 mL), drying over $MgSO_4$ and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with petroleum ether→70:30 petroleum ether/EtOAc) gave the title compound **5** as a white solid (1.85 g, 88%). Mp 112–118 °C; $[\alpha]_D^{27}$ −76.9 (*c* 0.5, $CHCl_3$); IR (neat): ν_{max} 3270 (br), 2932 (m), 2859 (w), 1681 (s), 1515 (m), 1453 (m), 1320 (s), 1256 (m), 1156 (s), 1080 (m), 964 (w), 907 (m), 792 (m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.35 (1H, t, *J*=2.0 Hz), 8.01 (2H, dd, *J*=8.0, 2.0 Hz), 7.60 (1H, t, *J*=8.0 Hz), 5.98 (2H, d, *J*=5.5 Hz), 4.48 (2H, d,

J=5.5 Hz), 3.39–3.26 (2H, m), 3.04–2.92 (2H, m), 2.05–1.89 (4H, m), 1.75–1.60 (4H, m), 1.42 (18H, s), 1.32–1.10 (8H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.4, 143.2, 130.3, 130.1, 125.5, 80.5, 60.2, 53.6, 34.1, 32.7, 28.5, 24.8, 24.5; ESMS: (m/z)=631 $[M+H]^+$, 653 $[M+Na]^+$; HRMS (ES): calcd for $C_{28}H_{47}N_4O_8S_2$ ($[M+H]^+$) 631.2830, found 631.2827; calcd for $C_{28}H_{46}N_4NaO_8S_2$ ($[M+Na]^+$) 653.2649, found 653.2635.

4.3.7. (*5*)·2TFA salt

A solution of bis-sulfonamide **5** (898 mg, 1.42 mmol) in 4:1 CH_2Cl_2/TFA (20 mL) was stirred for 4 h at room temperature. Toluene was added and the solvent was removed in vacuo. Trituration of the oily residue obtained with CH_2Cl_2 gave the title compound as an off-white solid, collected by filtration (917 mg, 98%). Mp 162–165 °C; $[\alpha]_D^{27}$ −64.1 (c 0.5, MeOH); IR (neat): ν_{max} 3086 (br), 2937 (m), 2865 (m), 1666 (s), 1516 (w), 1331 (m), 1126 (s), 796 (m) cm^{-1}; ^{1}H NMR (400 MHz, MeOD-d_4): δ 8.42 (1H, t, J=2.0 Hz), 8.19 (2H, dd, J=8.0, 2.0 Hz), 7.86 (1H, t, J=8.0 Hz), 3.18–3.07 (2H, m), 2.91 (2H, dt, J=4.0, 11.5 Hz), 2.14–2.04 (2H, m), 1.79–1.69 (2H, m), 1.63–1.54 (2H, m), 1.44 (2H, dq, J=3.5, 12.5 Hz), 1.35–1.03 (8H, m); ^{13}C NMR (100 MHz, MeOD-d_4): δ 144.3, 132.1, 132.0, 126.4, 56.6, 55.9, 32.3, 30.7, 25.4, 24.6; ESMS: (m/z)=431 $[M+H]^+$, 453 $[M+Na]^+$.

4.3.8. Macrocycle *8*

A solution of (**5**)·2TFA salt (216 mg, 0.328 mmol) and Et_3N (220 μL, 1.58 mmol) in MeCN (4 mL), and a solution of succinyl dichloride (37 μL, 0.336 mmol) in dry MeCN (4 mL) were added simultaneously, via syringe pump, into a flask equipped with condensor and $CaCl_2$ drying tube containing MeCN (60 mL) at 60 °C over 4 h. The resultant mixture was stirred overnight at 60 °C before cooling and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with CH_2Cl_2→96:4 CH_2Cl_2/MeOH) and recrystallisation (MeOH) gave the title compound **8** as a crystalline powder (34 mg, 20%). Mp 185–190 °C (MeOH); $[\alpha]_D^{27}$ +31.5 (c 0.4, $CHCl_3$); IR (neat): ν_{max} 3251 (w), 3076 (w), 2930 (m), 2856 (w), 1633 (s), 1537 (s), 1434 (m), 1324 (s), 1172 (s), 1152 (s), 1072 (s), 906 (m) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (1H, t, J=1.5 Hz), 8.06 (2H, dd, J=8.0, 1.5 Hz), 7.68 (1H, t, J=8.0 Hz), 7.18 (2H, d, J=7.5 Hz), 6.10 (2H, d, J=5.5 Hz), 3.62–3.51 (2H, m), 3.21 (2H, sept, J=5.5 Hz), 2.43–2.32 (2H, m), 1.96–1.84 (4H, m), 1.84–1.66 (6H, m), 1.46 (2H, dq, J=3.0, 12.5 Hz), 1.40–1.20 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.2, 143.8, 130.0, 129.6, 124.9, 61.7, 51.9, 36.12, 32.3, 31.4, 24.6, 24.2; ESMS: (m/z)=513 $[M+H]^+$, 535 $[M+Na]^+$; HRMS (ES): calcd for $C_{22}H_{33}N_4O_6S_2$ ($[M+H]^+$) 513.1836, found 513.1837; calcd for $C_{22}H_{32}N_4NaO_6S_2$ ($[M+Na]^+$) 535.1655, found 535.1681.

4.3.9. Macrocycle *9*

A solution of (**5**)·2TFA salt (212 mg, 0.322 mmol) and Et_3N (225 μL, 1.61 mmol) in MeCN (4 mL), and a solution of glutaryl dichloride (42 μL, 0.329 mmol) in MeCN (4 mL) were added simultaneously, via syringe pump, into a flask equipped with condensor and $CaCl_2$ drying tube containing MeCN (60 mL) at 60 °C over 3.5 h. The resultant mixture was stirred overnight at 60 °C before cooling and concentration in vacuo. The residue was taken into ethyl acetate (60 mL) and washed $KHSO_4$ (40 mL of a 1 M aqueous solution), K_2CO_3 (30 mL of a 1 M aqueous solution) and brine (30 mL) before drying over $MgSO_4$ and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with ethyl acetate, then 97:3→96:4 CH_2Cl_2/MeOH) gave the title compound **9** as a white solid (48 mg, 28%). Mp 185–194 °C; $[\alpha]_D^{22}$ +45.2 (c 0.3, $CHCl_3$); IR (neat): ν_{max} 3249 (w), 2933 (m), 2860 (w), 1642 (s), 1532 (s), 1450 (m), 1323 (s), 1171 (s), 1152 (s), 1077 (s), 957 (w), 899 (w), 795 (w), 681 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.27 (1H, t, J=1.5 Hz), 8.02 (2H, dd, J=8.0, 1.5 Hz), 7.63 (1H, t, J=8.0 Hz), 6.05 (2H, d, J=8.0 Hz), 5.92 (2H, d, J=6.5 Hz), 3.74–3.70 (2H, m), 3.22–3.09 (2H, m), 2.50–2.40 (2H, m), 1.92–1.83 (2H, m), 1.83–1.72 (8H, m), 1.66–1.39 (4H, m), 1.38–1.24 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.5 (0), 143.5 (0), 130.6 (1), 130.4 (1), 124.9 (1), 61.4, 52.3, 35.8, 35.0, 32.4, 24.8, 24.5, 21.2; ESMS: (m/z) 527 $[M+H]^+$, 549 $[M+Na]^+$; HRMS (ES): calcd for $C_{23}H_{34}N_4NaO_6S_2$ ($[M+Na]^+$) 549.1812, found 549.1815.

4.3.10. (*S*)-2-[3-((*S*)-1-Carboxy-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyric acid (*10*)

A solution of benzene-1,3-disulfonyl chloride (3.55 g, 12.9 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of H-L-Val-OBn·TsOH (10.3 g, 27.1 mmol) and Et_3N (5.6 mL, 40 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was warmed to room temperature and stirred overnight under N_2. The mixture was then diluted with CH_2Cl_2 (150 mL) and washed with HCl (250 mL of a 2 M aqueous solution), K_2CO_3 (2×200 mL of a 1 M aqueous solution) and brine (200 mL) before drying over $MgSO_4$ and concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with 9:1→3:1 petroleum ether/EtOAc) gave (*S*)-2-[3-((*S*)-1-benzyloxycarbonyl-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyric acid benzyl ester (**10** R=Bn) as a colourless oil (5.74 g, 72%). $[\alpha]_D^{27}$ +4.3 (c 0.75, $CHCl_3$); IR (neat): ν_{max} 3272 (w), 2963 (w), 1729 (s), 1453 (m), 1334 (s), 1156 (s), 1135 (s), 913 (m), 681 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (1H, t, J=2.0 Hz), 7.88 (2H, dd, J=8.0, 2.0 Hz), 7.38 (1H, t, J=8.0 Hz), 7.29–7.24 (6H, m), 7.16–7.11 (4H, m), 5.27 (2H, d, J=10.0 Hz), 4.88 (2H, d, J=12.0 Hz), 4.84 (2H, d, J=12.0 Hz), 3.80 (2H, dd, J=10.0, 5.0 Hz), 2.10–1.96 (2H, m), 0.89 (6H, d, J=7.0 Hz), 0.76 (6H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.0, 141.4, 134.9, 131.1, 130.1, 128.8, 128.7, 126.1, 67.7, 61.3, 31.8, 19.1, 17.3; ESMS: (m/z) 615 $[M-H]^-$. A mixture of (*S*)-2-[3-((*S*)-1-benzyloxycarbonyl-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyric acid benzyl ester prepared above (5.48 g, 8.89 mmol) and Pd/C (10% wt, 976 mg, 0.917 mmol) in MeOH (60 mL) was stirred at room temperature under H_2 (~1 atm balloon) for 4 h. The mixture was then filtered through a Celite™ pad and the filtrate concentrated in vacuo to give the title compound **10** as a white powder without further purification (3.76 g, 97%). Mp 200–203 °C; $[\alpha]_D^{27}$ +23.8 (c 0.5, MeOH); IR (neat): ν_{max} 3264 (m), 2969 (w), 1713 (s), 1668 (m), 1460 (w), 1413 (m), 1347 (s), 1219 (m), 1142 (s), 1051 (s), 897 (m), 795 (s), 678 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.24 (2H, d, J=8.5 Hz), 8.16 (1H, t, J=2.0 Hz), 7.97 (2H, dd, J=8.0, 2.0 Hz), 7.74 (1H, t, J=8.0 Hz), 3.54 (2H, t, J=7.0 Hz), 1.95 (2H, oct, J=7.0 Hz), 0.80 (6H, d, J=7.0 Hz), 0.76 (6H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.1, 142.0, 130.0, 130.0, 124.5, 61.4, 30.3, 18.9, 17.8; ESMS: (m/z) 435 $[M-H]^-$, 871 $[2M-H]^-$. HRMS (ES): calcd for $C_{16}H_{24}N_2O_8S_2Na$ ($[M+Na]^+$) 459.0866, found 459.0865.

4.3.11. *N*-Benzyl-(*S*)-2-[3-((*S*)-1-benzylcarbamoyl-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyramide (*12*)

A solution of (*S*)-2-[3-((*S*)-1-carboxy-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyric acid **10** (97 mg, 0.22 mmol) and carbonyldiimidazole (73 mg, 0.45 mmol) in THF (7 mL) was stirred at room temperature for 1 h. The mixture was then added to a solution of benzylamine (62 μL, 0.57 mmol) and Et_3N (50 μL, 0.36 mmol) in THF (5 mL) and the resulting mixture stirred overnight at room temperature, under N_2 before concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with 7:3→5.5:4.5 petroleum ether/EtOAc) gave the title compound **12** as a white solid (87 mg, 64%). Mp 90–92 °C; $[\alpha]_D^{25}$ +33.2 (c 0.25, MeCN); IR (neat): ν_{max} 3272 (w), 2966 (w), 1651 (s), 1539 (w), 1455 (w), 1434 (w), 1327 (s), 1156 (s), 1142 (s), 1080 (m), 1030 (w), 915 (w), 795 (m) cm^{-1}; ^{1}H NMR (400 MHz, MeCN-d_3): δ 8.26 (1H, t, J=2.0 Hz), 7.99 (2H, dd, J=8.0, 2.0 Hz), 7.61 (1H, t, J=8.0 Hz), 7.32–7.21 (6H, m), 7.12–7.07 (4H, m), 6.92 (2H, apparent t, J=6.0 Hz), 6.11 (2H, br s), 4.14 (2H, dd, J=15.0, 6.0 Hz), 4.04 (2H, dd, J=15.0, 6.0 Hz), 3.57 (2H, d, J=6.0 Hz), 1.97–1.88 (2H,

m), 0.83 (6H, d, J=7.0 Hz), 0.82 (6H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, MeCN-d_3): δ 170.8, 142.4, 139.6, 131.8, 131.2, 129.4, 128.4, 128.1, 126.7, 63.1, 42.7, 32.5, 19.5, 17.9; ESMS: (m/z) 615 $[M+H]^+$, 637 $[M+Na]^+$; HRMS (ES): calcd for $C_{30}H_{39}N_4O_6S_2$ ($[M+H]^+$) 615.2306, found 615.2301; calcd for $C_{30}H_{38}N_4NaO_6S_2$ ($[M+Na]^+$) 637.2125, found 637.2176.

4.3.12. 3-Methyl-(S)-2-[3-(2-methyl-(S)-1pentafluorophenyl oxycarbonyl-propylsulfamoyl)benzenesulfonylamino]-butyric acid pentafluorophenyl ester (**11**)

A solution of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.76 g, 9.19 mmol) in CH_2Cl_2 (35 mL) was added, dropwise over 30 min, to a solution of (*S*)-2-[3-((*S*)-1-carboxy-2-methyl-propylsulfamoyl)-benzenesulfonylamino]-3-methyl-butyric acid (**10**) (1.95 g, 4.46 mmol) and pentafluorophenol (2.10 g, 11.4 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The mixture was then warmed to room temperature and stirred overnight under N_2 before washing with $NaHCO_3$ (2×150 mL of a 5% w/v aqueous solution), drying over $MgSO_4$ and concentration in vacuo. The residue obtained was taken into EtOAc and filtered through a small silica pad before concentration of the filtrate in vacuo to give the title compound **11** as a white solid, which was used directly and not purified further (2.60 g, 76%). Mp 55–61 °C; $[\alpha]_D^{27}$ +16.2 (c 0.5, $CHCl_3$); IR (neat): ν_{max}=3285 (w), 2972 (w), 1784 (m), 1518 (s), 1741 (w), 1338 (m), 1158 (m), 1085 (s), 992 (s), 921 (w), 893 (w), 799 (w), 682 (m) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.45 (1H, t, J=2.0 Hz), 8.05 (2H, dd, J=8.0, 2.0 Hz), 7.66 (1H, t, J=8.0 Hz), 5.77 (2H, d, J=5.0 Hz), 4.25 (2H, dd, J=10.0, 5.0 Hz), 2.43–2.28 (2H, m), 1.10 (6H, d, J=7.0 Hz), 0.97 (6H, d, J=7.0 Hz).

4.3.13. Macrocycle **13**

A solution of pentafluorophenol ester **11** (209 mg, 0.27 mmol) and TBACl (149 mg, 0.534 mmol) in CH_2Cl_2 (4 mL), and a solution of 1,5-diaminopentane (32 μL, 0.27 mmol) and Et_3N (114 μL, 0.82 mmol) in CH_2Cl_2 (4 mL) were added simultaneously, via syringe pump, into CH_2Cl_2 (20 mL) at room temperature over a period of 1.75 h before stirring at room temperature overnight. The mixture was then concentrated in vacuo. Purification by flash column chromatography (SiO_2 eluted with 1:1→3:1 EtOAc/petroleum ether) gave the title compound **13** (108 mg, 79%). Mp 160–162 °C; $[\alpha]_D^{26}$ +144 (c 0.5, MeCN); IR (neat): ν_{max} 3409 (w), 3375 (w), 3271 (w), 2965 (w), 2936 (w), 1659 (s), 1538 (m), 1440 (w), 1414 (w), 1341 (s), 1329 (s), 1175 (s), 1130 (m), 1053 (m), 934 (w), 919 (w), 801 (m), 682 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.15 (1H, t, J=2.0 Hz), 8.09 (2H, d, J=9.0 Hz), 7.96 (2H, dd, J=8.0, 2.0 Hz), 7.80 (2H, dd, J=7.0, 4.5 Hz), 7.67 (1H, t, J=8.0 Hz), 3.54 (2H, dd, J=9.0, 7.0 Hz), 3.20–3.09 (2H, m), 2.67–2.57 (2H, m), 1.89 (2H, oct, J=7.0 Hz), 1.24–1.11 (2H, m), 1.11–1.00 (2H, m), 0.91 (6H, d, J=7.0 Hz), 0.88 (6H, d, J=7.0 Hz), 0.69 (2H, quin, J=7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.5, 142.7, 129.7, 129.2, 124.4, 61.7, 38.1, 31.1, 28.1, 23.3, 19.1, 18.2; ESMS: (m/z)=503 $[M+H]^+$, 525 $[M+Na]^+$; HRMS (ES): calcd for $C_{21}H_{35}N_4O_6S_2$ ($[M+H]^+$) 503.1993, found 503.2014; calcd for $C_{21}H_{34}N_4NaO_6S_2$ ($[M+Na]^+$) 525.1812, found 525.1815.

4.3.14. Macrocycle **14**

A solution of pentafluorophenol ester **11** (677 mg, 0.881 mmol) and TBACl (500 mg, 1.80 mmol) in CH_2Cl_2 (5 mL), and a solution of *m*-xylylenediamine (120 μL, 0.909 mmol) and Et_3N (500 μL, 3.59 mmol) in CH_2Cl_2 (5 mL) were added simultaneously, via syringe pump, into CH_2Cl_2 (100 mL) at room temperature over a period of 5 h before stirring at room temperature overnight. The mixture was then concentrated in vacuo. Purification by flash column chromatography (SiO_2 eluted with 4:6→5.5:4.5 EtOAc/petroleum ether) gave the title compound **14** as a white solid (280 mg, 59%). Mp >240 °C (MeOH) (decomposes); $[\alpha]_D^{26}$ +195 (c 0.5, DMSO); IR (neat): ν_{max} 3599 (w), 3488 (w), 3238 (m), 3090 (w), 2968 (w), 2873 (w), 1688 (m), 1651 (s), 1548 (m), 1462 (m), 1454 (m), 1325 (s), 1269 (w), 1224 (w), 1178 (s), 1128 (m), 1089 (m), 1050 (m), 803 (m), 793 (m), 719 (w), 703 (w), 680 (m) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.42 (2H, dd, J=7.0, 4.0 Hz), 8.13 (2H, br s), 7.98 (1H, s), 7.62 (2H, dd, J=8.0, 1.5 Hz), 7.33 (1H, t, J=7.5 Hz), 7.21 (2H, d, J=7.5 Hz), 6.77 (1H, t, J=8.0 Hz), 6.75 (1H, s), 4.34 (2H, dd, J=14.0, 7.0 Hz), 3.75 (2H, dd, J=14.0, 4.0 Hz), 3.62 (2H, br s), 1.92 (2H, oct, J=7.0 Hz), 0.95 (6H, d, J=7.0 Hz), 0.94 (6H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.4, 142.5, 138.6, 128.9, 128.5, 128.3, 128.0, 127.6, 123.3, 61.9, 42.4, 31.3, 19.1, 18.3; ESMS: (m/z) 537 $[M+H]^+$, 559 $[M+Na]^+$; HRMS (ES): calcd for $C_{24}H_{32}N_4NaO_6S_2$ ($[M+Na]^+$) 559.1655, found 559.1666.

4.3.15. 5-Octyloxy-isophthalic acid (**15**)

A mixture of dimethyl-5-hydroxyisophthalate (6.20 g, 29.5 mmol), 1-iodooctane (5 mL, 27.5 mmol) and K_2CO_3 (13.9 g, 100.3 mmol) in acetone (140 mL) was heated to reflux overnight. The mixture was then filtered and the filtrate concentrated in vacuo. CH_2Cl_2 was added to the residue and insoluble material removed by filtration before concentration of the filtrate in vacuo once more. The crude material was then taken into 1,4-dioxane/1.5 M aqueous LiOH (200 mL of a 1:1 mixture) and stirred overnight. This mixture was washed with Et_2O (2×200 mL) and acidified with 3 M aqueous $KHSO_4$ solution. A white precipitate was observed and was collected by filtration, washed consecutively with CH_2Cl_2 and H_2O and suspended in toluene. Concentration in vacuo gave the title compound **15** as a white solid (5.81 g, 72%). Mp 225–227 °C; IR (neat): ν_{max} 2923 (m), 2855 (m), 2566 (w), 1705 (s), 1683 (s), 1595 (m), 1643 (m), 1413 (m), 1338 (m), 1309 (m), 1271 (s), 1125 (w), 1044 (m), 929 (m), 908 (m), 759 (s), 734 (s), 685 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 13.20 (2H, br s), 8.06 (1H, t, J=1.5 Hz), 7.62 (2H, d, J=1.5 Hz), 4.06 (2H, t, J=6.5 Hz), 1.78–1.66 (2H, m), 1.47–1.20 (10H, m), 0.85 (3H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.4, 158.8, 132.6, 122.1, 119.0, 68.1, 31.2, 28.6, 28.6, 28.5, 25.4, 22.0, 13.9; ESMS: m/z=293 $[M-H]^-$, 587 $[2\,M-H]^-$. Anal. Calcd for $C_{16}H_{22}O_5$: C, 65.29; H, 7.53. Found: C, 65.28; H, 7.52.

4.3.16. 3-Aminomethyl-5-octyloxy-benzylamine (**16**)

A mixture of 5-octyloxy-isophthalic acid **15** (5.47 g, 18.6 mmol) and PCl_5 (10 g, 48 mmol) was stirred at 180 °C until a homogeneous yellow solution was formed. The mixture was then cooled to room temperature and carefully added into NH_3 saturated CH_2Cl_2 (250 mL) at 0 °C. A white precipitate was formed immediately, which was collected by filtration, washed with H_2O and suspended in toluene. Concentration in vacuo gave 5-octyloxy-isophthalamide as a white solid (4.53 g, 83%). Mp 200–203 °C; IR (neat): ν_{max} 3400 (m), 3323 (w), 3418 (w), 3142 (w), 2951 (w), 2918 (m), 2871 (w), 2850 (w), 1692 (s), 1652 (s), 1625 (s), 1593 (s), 1470 (w), 1432 (s), 1394 (s), 1375 (s), 1255 (m), 1090 (w), 1048 (m), 882 (m), 782 (m), 675 (m), 639 (m) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.99 (2H, br s), 7.96 (1H, t, J=1.5 Hz), 7.53 (2H, d, J=1.5 Hz), 7.40 (2H, br s), 4.04 (2H, t, J=6.5 Hz), 1.79–1.67 (2H, m), 1.48–1.22 (10H, m), 0.86 (3H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 158.5, 135.7, 119.0, 116.0, 67.9, 31.2, 28.7, 28.6, 28.6, 25.4, 22.0, 13.9; ESMS: (m/z) 315 $[M+Na]^+$. HRMS (ES): calcd for $C_{16}H_{25}N_2O_3$ ($[M+H]^+$) 293.1860, found 293.1861. A mixture of 5-octyloxy-isophthalamide prepared above (1.98 g, 6.77 mmol) and $LiAlH_4$ (1.12 g, 29.6 mmol) in THF (125 mL) was stirred under N_2 at room temperature for 30 min before warming to reflux for 2.5 h. The mixture was then cooled before addition of H_2O (100 mL) and concentration in vacuo. The residue was extracted with CH_2Cl_2 (2×100 mL) and the combined organic layers dried over $MgSO_4$ before concentration in vacuo. The residue was taken into HCl (50 mL of a 1 M aqueous solution) and washed with Et_2O (3×50 mL), basified with NaOH (60 mL of a 2 M aqueous solution)

before re-extraction with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo to give the title compound **16** as a yellow oil, which was used in the following reaction without further purification. (915 mg, 51%). IR (neat): ν_{max} 3358 (w), 2922 (s), 2854 (s), 1673 (w), 1593 (s), 1452 (s), 1378 (m), 1326 (m), 1287 (s), 1162 (s), 1053 (m), 976 (m), 836 (s), 702 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.84 (1H, s), 6.74 (2H, s), 3.96 (2H, t, J=6.5 Hz), 3.82 (4H, s), 1.81–1.72 (2H, m), 1.49–1.39 (2H, m), 1.39–1.21 (8H, m), 0.88 (3H, t, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9, 145.3, 118.0, 111.7, 68.2, 46.7, 32.0, 29.5, 29.4, 29.4, 26.2, 22.8, 14.2; ESMS: (m/z) 265 $[M+H]^+$, 287 $[M+Na]^+$.

4.3.17. *Macrocycle* **17**

A solution of pentafluorophenol ester **11** (682 mg, 0.888 mmol) and TBACl (501 mg, 1.80 mmol) in CH_2Cl_2 (5 mL), and a solution of 3-aminomethyl-5-octyloxy-benzylamine **16** (239 mg, 0.904 mmol) and Et_3N (500 μL, 3.59 mmol) in CH_2Cl_2 (5 mL) were added simultaneously, via syringe pump, into CH_2Cl_2 (100 mL) at room temperature over a period of 5 h. The mixture was then stirred overnight before concentration in vacuo. Purification by flash column chromatography (SiO_2 eluted with 8.5:1.5→6.5:3.5 petroleum ether/EtOAc) and precipitation from EtOAc/petroleum ether gave the title compound **17** as a white, flocculent solid (246 mg, 42%). Mp 130–132 °C (EtOAC/petroleum ether); $[\alpha]_D^{26}$ +185 (*c* 0.25, MeCN); IR (neat): ν_{max} 3361 (w), 2929 (m), 1661 (s), 1598 (m), 1539 (m), 1456 (s), 1325 (s), 1297 (s), 1219 (w), 1174 (s), 1156 (s), 1125 (s), 1082 (s), 919 (m), 860 (m), 794 (s), 720 (m), 681 (m) cm^{-1}; ^1H NMR (400 MHz, MeCN-d_3): δ 8.11 (1H, t, J=2.0 Hz), 7.64 (2H, dd, J=8.0, 2.0 Hz), 6.98–6.91 (2H, m), 6.95 (1H, t, J=8.0 Hz), 6.75 (2H, d, J=1.5 Hz), 6.42 (1H, t, J=1.5 Hz), 6.15 (2H, br s), 4.37 (2H, dd, J=14.0, 8.0 Hz), 4.03 (2H, t, J=6.5 Hz), 3.81 (2H, dd, J=14.0, 4.5 Hz), 3.65 (2H, br s), 2.05–1.96 (2H, m), 1.85–1.76 (2H, m), 1.54–1.44 (2H, m), 1.43–1.24 (8H, m), 1.01 (6H, d, J=7.0 Hz), 0.94 (6H, d, J=7.0 Hz), 0.89 (3H, t, J=7.0 Hz); ^{13}C NMR (100 MHz, MeCN-d_3): δ 170.6, 160.1, 143.1, 141.2, 130.6, 130.2, 125.7, 121.4, 114.6, 68.9, 62.9, 43.9, 33.1, 32.6, 30.1, 30.0, 26.8, 23.4, 19.6, 17.9, 14.4; ESMS: (m/z)=687 $[M+Na]^+$; HRMS (ES): calcd for $C_{32}H_{48}N_4NaO_7S_2$ ($[M+Na]^+$) 687.2857, found 687.2862.

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Supplementary data

^1H NMR titration data for receptors **6**–**9**, **12**–**14** and **17**, ^1H and ^{13}C NMR spectra for all compounds reported in the manuscript. Crystallographic data for the structures in this manuscript have been deposited with the Cambridge Crystallographic Data Centre with deposition numbers CCDC 706271–706273. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.01.070.

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