SUPPORTING INFORMATION


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1.- Theoretical Studies on the Conformation adopted by the Receptor 100 free in water

To the best of our knowledge, the conformational preference of the tetra-α isomers of aryl-extended calix[4]pyrroles and their cavitand derivatives in water has not been investigated. We are aware of three theoretical studies addressing the conformational dynamics of octamethyl-calix[4]pyrrole.\textsuperscript{1,2,3}

![Figure S1](image)

Figure S1: Center: side views of the energy minimized structures of the 100 receptor: a) in cone conformation and b) in 1,3 alternate conformation (PB86-D3-def2-SVP). The receptor is shown in stick representation. Only polar hydrogens are shown for clarity. The structures were energy-minimized with four explicit hydrogen-bonded water molecules to avoid the collapse of the aromatic cavities. Water molecules are shown as yellow CPK models. Left and right columns: top and bottom views, respectively, of the central structure rotated 90° and depicted as CPK models.

These studies concluded that in all investigated solvents octamethyl-calix[4]pyrrole prefers to adopt a 1,3-alternate conformation (> 60%) with an increase of other conformations in polar solvents. Furthermore, the 1,3-alternate conformer experienced and extremely rapid change to the cone conformation upon anion binding. The non-conformational preorganization of the host did not seemed to be a major impediment for anion binding. Using the same level of theory employed in the study of the structure of the 6c-100 complex with an implicit model of water solvation, we computed the energies of the cone and 1,3-alternate conformers of free 100, 110 and 3. This procedure led to a significant collapse of the aromatic cavity of the cone conformers and severe planarity distortion of the pyrrole rings. For this reason, we performed the energy minimization of the cone and 1,3-alternate conformers using four explicit water molecules, which are hydrogen bonded to the pyrrole NHs. The molecular modelling studies revealed that the cone conformation of the newly described receptors (cavitand 1 and aryl-extended calix[4]pyrrole 3) is slightly more favourable energetically in water than the 1,3-alternate counterpart. In the case of the 100 receptor, the cone conformer was energetically favoured by 4.1 Kcal/mol with respect to the 1,3-alternate.

In striking contrast, the noticeable chemical shift changes experienced by the β-pyrrole protons of the aryl-extended calix[4]pyrroles and cavitand receptors upon guest-binding (see previous section) hinted to a complexation-induced conformational change of the receptor. We reconcile experiment and theory by assuming the existence of an equilibrium between both conformers of the free host in water solution. This equilibrium features a fast chemical exchange on the chemical shift timescale owing to a low energy barrier for the interconversion.
2.- Assessment of the Thermodynamic Constants for the 1:1 Complexes.

'H NMR titrations. The binding constants of the 1:1 complexes displaying fast chemical exchange on the chemical shift time scale were determined using the HypNMR 2008 software package. We performed non-linear fits of the experimentally measured chemical shift changes of diagnostic proton signals of the receptor to a theoretical 1:1 binding isotherm. In all cases, the obtained fits were very good (small residuals) returning the values of $K_a$ and $\delta_{\text{bound}}$. Because the magnitudes of the binding constant values were smaller than $10^4$ M$^{-1}$, it was possible to determine them accurately using this titration technique.

Isothermal titration calorimetry (ITC) experiments. For the complexes exhibiting slow chemical exchange on the chemical shift timescale with the free counterparts, the corresponding binding constants were assessed using isothermal titration calorimetry (ITC) experiments. Titrations were performed using non-buffered MilliQ water (cavities 100, 110, 2 and aryl-extended calix[4]pyrrole 3) or chloroform solutions (1700). The calix[4]pyrrole host was placed in the calorimeter’s cell and a 7-10-fold more concentrated solution of the guest in the same solvent was injected in small aliquots (~5 µL) using a computer controlled syringe. An ITC experiment affords, in a single run, direct information on the enthalpy, binding stoichiometry and association constant value. From the experimentally determined values ($\Delta H$ and $K_a$), the entropy ($\Delta S$) and the free energy of binding ($\Delta G$) are easily derived. All performed ITC experiments showed very good fits to the theoretical binding isotherm for 1:1 complex formation. The titration data were fitted using the “one set of sites” binding model implemented in the Microcal Data Analysis software.

Presentation of the thermodynamic data. To facilitate the analysis of the thermodynamic data and the subsequent drawing of conclusions, the measured binding constant values using either 'H NMR spectroscopic titrations or ITC experiments ($K_a$), the derived Gibbs free energies ($\Delta G$) and the enthalpy ($\Delta H$) and entropy ($\Delta S$) terms for the binding processes studied using ITC experiments are summarized in separate tables in the text of the manuscript.

3.- General information and instrumentation

Reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All solvents were commercially obtained and used without further purification except pyrrole, which was distilled and stored in the freezer for further use. Dry solvents were taken from a solvent system MB SPS 800. THF, Et3N, were dried and distilled. Routine 'H NMR and $^{13}$C NMR spectra were recorded on a Bruker Avance 300 (300 MHz for 'H NMR and 75 MHz for $^{13}$C NMR), Bruker Avance 400 (400 MHz for 'H NMR and 100 MHz for $^{13}$C NMR), Bruker Avance 500 (500 MHz for 'H NMR and 125 MHz for $^{13}$C NMR) or Bruker Avance 500 with cryoprobe (500 MHz for 'H NMR and 125 MHz for $^{13}$C NMR). Deuterated solvents (SigmaAldrich) used are indicated in the characterization and chemical shifts are given in ppm. Residual solvent peaks were used as reference. All NMR J values are given in Hz. COSY, NOESY, HMOC and HMBC experiments were recorded to help with the assignation of 'H and $^{13}$C signals. Isothermal titration calorimetry experiments (ITC) were performed using a Microcal VP-ITC Microcalorimeter. High Resolution Mass Spectra were obtained on a Bruker HPLC-TOF (MicroTOF Focus) with ESI as ionization mode and Bruker HPLC-QqTOF (MaXis Impact) with ESI as ionization mode. Crystal structure determinations were carried out using Bruker Apex II Duo diffractometer with MoKα radiation and Rigaku MicroMax-007HF diffractometer with MoKα radiation. Crystal structure solution was achieved using direct methods as implemented in SHELX-2014. Least-squares refinement on F$^2$ using all measured intensities was carried out using the program SHELX-2014. Column chromatography was performed with silica gel technical grade (Sigma-Aldrich), pore size 60 Å, 230-400 mesh particle size, 40-63 μm particle size. TLC plates were silica gel 60 F254.
4.- Experimental procedures and characterization.

4.1.- Synthesis and characterization of ketone 14a

![Scheme 5: Synthetic scheme for the preparation of ketone 14a. The proton assignment is indicated in the molecular structure of 14a.]

The synthesis of the ketone involves two steps. All procedures were carried out under argon atmosphere. Step a') formation of the acyl chloride. To a 150 mL solution of 3-methoxy-4-methylbenzoic acid 13a (10 g, 60.2 mmol) in dry toluene, 26.3 mL of thionyl chloride (43.0 g, 361 mmol, 6 eq) and 5 droplets of DMF were added. The reaction mixture was refluxed at 125 °C for 3 hours. Then, the reaction was cooled down to room temperature and dried under reduced pressure obtaining a light yellow oil. This oil was used directly in the next step.

*Step a*) Grignard addition. The readily prepared acyl chloride and tris(acetylacetonato) iron(III) (0.638 g, 1.806 mmol, 0.03 eq.) were dissolved in 20 mL of dry THF (distilled over Na). Then, the 4-chlorobutyl) magnesium bromide (11.79 g, 60.2 mmol, 1 eq.) was added via cannula at -78 °C and left at the same temperature for 30 min. The reaction mixture changed the colour from orange to dark brown. After that, the reaction mixture was warmed up to room temperature and left stirring overnight. Next morning, the reaction mixture was orange. To quench the reaction first water and then NaOH (2M) were added. The water phase was extracted 3 times with DCM. The organic phase was dried with Na2SO4, filtered, and concentrated under reduced pressure obtaining a red oil. The crude was purified by silica gel column chromatography using DCM:Hex (95:5) as an eluent. The desired fractions were concentrated under vacuum obtaining 7.1 g of a light yellow oil as the final product. 58% yield (referred to starting material).

1H NMR (400 MHz, (CD)3CO, 25 °C): δ (ppm) 7.55 (dd, J=7.5 Hz, J=1.5Hz, 1H, H8), 7.49 (d, J=1.5 Hz, 1H, Hb), 7.26 (d, J=7.5 Hz, 1H, Hc), 3.90 (s, 3H, OCH3), 3.66 (t, J=6.1 Hz, 2H, CH2CH2CH2CH2Cl), 3.07 (t, J=7.1 Hz, 2H, CH2CH2CH2CH2Cl), 2.23 (s, 3H, p-CH3) 1.85 (m, 4H, CH2CH2CH2CH2Cl).

13C NMR (100 MHz, (CD)3CO, 25 °C): δ (ppm) 199.5, 159.0, 137.6, 133.1, 131.4, 121.7, 109.6, 55.9, 45.8, 38.1, 33.1, 22.54, 16.65.

HR-MS (HPLC-ESI-TOF) (C13H18ClO2) Meas. m/z = 241.0991 [M+H]+; m/z = 241.0990.
Figure S2: $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, 25°C) of the ketone 14a.

Figure S3: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25°C) of the ketone 14a.

Figure S4: HR-MS spectrum of 14a (left) and theoretical isotopic pattern (right).
4.2. Synthesis and characterization of ketone 15a

\[ \text{Scheme S2: Synthetic scheme for the preparation of ketone 15a. Proton assignment is indicated in the molecular structure of 15a.} \]

The synthesis of the final ketone involves two steps. **Step b) demethylation of the ether.** 14a (7 g, 30.9 mmol) was dissolved in 41 mL of acetic acid and 41 mL of hydrobromic acid and refluxed at 130 °C overnight. The reaction mixture turned dark red/brown. Next day, the reaction was cooled down to room temperature. The reaction mixture was then diluted with water and extracted three times with DCM. The organic layer was neutralized with NaHCO₃ and extracted again three times with DCM. The organic phase was dried with Na₂SO₄, filtered and concentrated under reduced pressure to obtain a brown solid.

**Step c) bromo-chloro exchange.** In the previous reaction, the terminal chlorine was substituted by bromine under reaction conditions. To recover the desired functionalization, all the brown solid obtained in the last step was dissolved together with trybuthylmethyl ammonium chloride (1.122 g, 4.76 mmol, 0.3 eq) in 150 mL of DCE and refluxed at 100 °C overnight. Next day, the reaction mixture was cooled down to room temperature and diluted with water. The organic phase was extracted three times using DCM. After that, the organic phase was washed with water, dried with Na₂SO₄, filtered, and concentrated under reduced pressure. The crude was purified by silica gel column chromatography using DCM:EtOAc (95:5) as an eluent. The desired fractions were concentrated under vacuum obtaining 3 g of a yellow solid as a final product. 62% yield (referred to starting material).

\(^1^H\) NMR (400 MHz, (CD)₃CO, 25 °C): δ (ppm) 8.52 (s, 1H, ArOH), 7.44 (d, J=1.5 Hz, 1H, H₆), 7.43 (dd, J=7.5 Hz, J=1.5 Hz, 1H, H₅), 7.21 (d, J=7.5 Hz, 1H, H₄), 3.64 (t, J=6.1 Hz, 2H, CH₂CH₂CH₂CH₂Cl), 2.99 (t, J=7.1 Hz, 2H, CH₂CH₂CH₂CH₂Cl), 2.25 (s, 3H, p-CH₃), 1.83 (m, 4H, CH₂CH₂CH₂CH₂Cl).

\(^1^3^C\) NMR (400 MHz, (CD)₃CO, 25 °C): δ (ppm) 199.3, 156.4, 137.3, 131.6, 131.1, 120.5, 114.3, 45.6, 37.9, 32.9, 22.4, 16.3.

**HR-MS** (HPLC-ESI-TOF) (C₁₂H₁₅NaClO₂) Meas. m/z = 249.0646 [M+H]+; m/z = 249.0653.

![Figure S5: \(^1^H\) NMR (400 MHz, (CD)₃CO, 25 °C) of the ketone 15a](image-url)
4.3.- Synthesis and characterization of ketone 14b

Scheme S3: Synthetic scheme for the preparation of ketone 14b. Proton assignment is indicated in the molecular structure of the ketone.

The commercially available acyl chloride 13b (2.54 mL, 19.4 mmol) and tris(acetylacetonato) iron(III) (0.206 g, 0.582 mmol, 0.03 eq.) were dissolved in 39 mL of dry THF (distilled over Na). Then, the (4-
chlorobutyl) magnesium bromide (3.8 g, 19.4 mmol, 1 eq.) was added via cannula at –78 °C and left at the same temperature for 30 min. The reaction mixture changes the colour from orange to dark brown. After that, the reaction mixture was warmed up to room temperature and left stirring overnight. Next morning, the reaction mixture was brown. To quench the reaction first water and then NaOH (2 M) were added. The water phase was extracted 3 times with DCM. The organic extracts were dried with Na2SO4, filtered and concentrated under reduced pressure, obtaining a red oil. The crude was purified by silica gel column chromatography using DCM:Hx (95:5) as an eluent. The desired fractions were concentrated under vacuum obtaining 2.5 g of a white solid as the final product. 61% yield.

1H NMR (300 MHz, CDCl3, 25 °C): δ (ppm) 7.87 (d, J ~8.1 Hz, 2H, Hα), 7.27 (d, J ~8.1 Hz, 2H, Hβ), 3.59 (t, J ~6.1 Hz, 2H, CH2CH2CH2CH2Cl), 2.95 (t, J ~6.1 Hz, 2H, CH2CH2CH2CH2Cl), 2.42 (s, 3H, p-CH3) 1.89 (m, 4H, CH2CH2CH2CH2Cl).

13C NMR (400 MHz, (CD3)2CO, 25 °C): δ (ppm) 199.5, 144.5, 135.8, 130.2, 129.1, 45.7, 38.1, 33.1, 22.4, 21.6.

NM (HPLC-APCI) (C12H16ClO) Meas. m/z = 211.1 [M+H]+.

**Figure S8:** 1H NMR (300 MHz, CDCl3, 25 °C) of the ketone 14b

**Figure S9:** 13C NMR (100 MHz, (CD3)2CO, 25 °C) of ketone 14b
4.4.- Synthesis and characterization of aryl-extended calix[4]pyrrole 16a


Ketone 15a (1g, 4.41 mmol) and tributyl methyl ammonium chloride (3.12 g, 13.23 mmol, 3 eq.) were dissolved in 9 mL of DCM under argon atmosphere. Once all was dissolved, pyrrole (0.296 g, 4.41 mmol, 1 eq.) was added followed by the dropwise addition of HCl 4M in dioxane (3.31 mL, 13.23 mmol, 3 eq.). The reaction was left stirring for 3 hours. After that, the reaction mixture was diluted with DCM and neutralized with NaHCO₃. The aqueous phase was extracted three times with DCM. The organic extracts were washed with water to ensure the removal of the salt, dried with Na₂SO₄, filtered, and concentrated under reduced pressure to obtain a dark brown oil. The crude was purified by silica gel column chromatography using DCM:AcO (98:2) as eluent. The desired fractions were concentrated under vacuum to provide 480 mg of a dark brown/orange solid as a final product. 10% yield.

H NMR (400 MHz, (CD₃)₂CO, 25 °C): δ (ppm) 8.51 (bs, 4H, NHs), 7.90 (s, 4H, ArOH), 6.98 (d, JHa-Hb~7.5 Hz, 4H, Ha), 6.43 (dd, JHb-Ha~7.5 Hz, JHb-Hc~1.5 Hz, 4H, Hb), 6.41 (d, JHc-Hb~1.5 Hz, 4H, Hc) 5.94 (d, JHd-NH~2.6, 8H, Hd), 3.54 (m, 8H, CH₂CH₂CH₂CH₂Cl), 2.32 (m, 8H, CH₃CH₂CH₂CH₂Cl), 2.11 (s, 12H, p-CH₃), 1.71 (m, 8H, CH₃CH₂CH₂CH₂Cl), 1.26 (m, 8H, CH₃CH₂CH₂CH₂Cl).

C NMR (100 MHz, (CD₃)₂CO, 25 °C): δ (ppm) 155.1, 145.9, 138.1, 123.3, 121.8, 116.5, 105.4, 48.8, 45.7, 40.7, 33.9, 23.3, 15.7.

HR-MS (HPLC-ESI-TOF) (C₆₄H₇₀Cl₄N₄O₄) Meas. m/z = 549.2094 [M-2H]⁺; m/z = 549.2081.
Figure S11: $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, 25 °C) of the aryl-extended calix[4]pyrrole 16a

Figure S12: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 °C) of the aryl-extended calix[4]pyrrole 16a

Scheme S5: synthetic scheme for the preparation of the aryl-extended calix[4]pyrrole 16b. Proton assignment is indicated in the molecular structure of 16b.

5-Chloro-1-(p-tolyl)pentan-1-one (1g, 4.75 mmol) and tributyl methyl ammonium chloride (3.36 g, 14.24 mmol, 3 eq.) were dissolved in 9.5 mL of DCM under argon atmosphere. Once all was dissolved, pyrrole (0.318 g, 4.75 mmol, 1 eq.) was added followed by the dropwise addition of HCl 4M in dioxane (3.56 mL, 14.24 mmol, 3 eq.). The reaction was left stirring for 5 hours. After that, the reaction mixture was diluted with DCM and neutralized with NaHCO₃. The aqueous phase was extracted three times with DCM. The organic extracts were washed with water to remove the salt, dried with Na₂SO₄, filtered and concentrated under reduced pressure to obtain a dark brown solid. The crude was purified by silica gel column chromatography using DCM:Hexane (50:50) as an eluent. The desired fractions were concentrated under vacuum to provide 185.2 mg of a white solid as a final product. 10% yield.

1H-NMR (400 MHz, CDCl₃, 25 °C): δ (ppm) 7.44 (bs, 4H, NHs), 7.00 (s, 16H, Hₐ + H₋), 5.88 (d, J_Hc-NH~2.6 Hz, 8H, Hc), 3.49 (m, 8H, CH₂CH₂CH₂CH₂Cl), 2.33 (s, 12H, p-CH₃), 2.29 (m, 8H, CH₂CH₂CH₂CH₂Cl), 1.75 (m, 8H, CH₂CH₂CH₂CH₂Cl), 1.40 (m, 8H, CH₂CH₂CH₂CH₂Cl).

13C-NMR (100 MHz, CDCl₃, 25 °C): δ (ppm) 141.6, 136.1, 135.7, 128.5, 106.2, 48.6, 44.9, 39.8, 33.2, 22.8, 21.1.

HR-MS (HPLC-ESI-TOF) (C₆₅H₇₃Cl₄N₄) Meas. m/z = 1307.4564 [M+H]+; m/z = 1037.4584.
Figure S14: $^1$H NMR (400 MHz, CDCl$_3$, 25 °C) of the aryl-extended calix[4]pyrrole 16b

Figure S15: $^{13}$C NMR (100 MHz, CDCl$_3$, 25 °C) of the aryl-extended calix[4]pyrrole 16b

Figure S16: HR-MS spectrum of 16b (left) and theoretical isotopic pattern (right).
4.6. Synthesis and characterization of bisphosphonate cavitands 17

Scheme S6: Synthetic scheme for the preparation of cavitands 17ii, 17io, and 17oo

In a Schlenk tube, the aryl-extended calix[4]pyrrole 16a (100 mg, 0.091 mmol) was dissolved in 5.5 mL of dry THF (distilled over Na) under argon atmosphere. Then, dry Et$_3$N (distilled over CaH$_2$) (253 µL, 1.815 mmol, 20 eq.) was added to the reaction mixture followed by the addition of ethylphosphonic dichloride (24.2 µL, 0.227 mmol, 2.5 eq.). The reaction mixture was stirred at room temperature for 4 hours. The reaction was quenched by the addition of water first and then some droplets of 10% HCl in order to quench the excess of Et$_3$N. The crude was extracted three times with DCM. The organic extracts were filtered, washed with water. The resulting organic phase was dried with Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to obtain a pale yellow solid. The crude was purified by silica gel column chromatography using DCM:EtOAc (95:5) as an eluent. The first product eluting from the column is the in-out isomer (io) and the last one is the out-out isomer (oo). Only traces of the in-in isomer (ii) were isolated. The desired fractions were concentrated under vacuum to obtain 27.2 mg of the io isomer as a colorless solid, 24% yield, and 23.8 mg of the oo isomer as a colorless solid, 21% yield.

4.6.1. Characterization of 17io:

$^1$H NMR (500 MHz, (CD$_3$)$_2$CO, 25 °C): δ (ppm) 8.73 (bs, 2H, NH$_a$), 8.39 (bs, 1H, NH$_b$) 8.28 (bs, 1H, NH$_c$), 7.39 (bs, 2H, H$_d$), 7.15 (bd, J=6.0 Hz, 2H, H$_e$), 7.12 (bd, J=4.8 Hz, 2H, H$_f$), 6.79 (bs, J=8.5 Hz, 2H, H$_g$), 6.70 (bs, 2H, H$_h$), 6.69 (bd, J=7.5 Hz, 2H, H$_i$), 6.04 (m, 4H, H$_j$ + H$_k$), 6.01 (d, J=2.6 Hz, 2H, H$_l$), 5.99 (d, J=2.6 Hz, 2H, H$_m$), 3.56 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$Cl), 2.47-2.12 (m, 24H, CH$_3$CH$_2$CH$_2$Cl + P(O)$_2$(CH$_3$)$_2$CH$_2$ (J=27.7 Hz) + p-(CH$_3$)$_2$ + p-(CH$_3$)$_2$), 1.72 (m, 8H, CH$_2$CH$_2$CH$_2$Cl), 1.46-1.14 (m, 14H, P(O)$_2$(CH$_3$)$_2$CH$_2$H$_2$ (J=21.8Hz) + CH$_2$CH$_2$CH$_2$Cl).

$^3$P NMR (160 MHz (CDCl$_3$, 25 °C)): δ (ppm) 29.2. 27.8.

$^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 °C): δ (ppm) 150.2, 148.8, 148.7, 145.7, 145.7, 137.4, 136.8, 136.8, 136.4, 131.1, 130.6, 129.4, 126.4, 126-3, 126.7, 126.5, 122.0, 119.9, 105.2, 105.1, 105.0, 48.1, 47.9, 44-7, 44-6, 39.8, 39.2, 33.0, 32.8, 22.4, 21.4, 20.4, 18.8, 16.6, 16.4, 15.0, 6.6, 6.5, 6.3, 6.2.

HR-MS (HPLC-ESI-TOF) (C$_{68}$H$_{79}$Cl$_2$N$_4$O$_6$P$_2$) Meas. m/z = 1249.4204 [M+H]$^+$; m/z = 1249.4223.
Scheme S7: Molecular structure of the cavitand 17io with proton assignment.

Figure S17: $^1$H NMR (500 MHz, (CD$_3$)$_2$CO, 25 °C) of the cavitand 17io
Figure S18: 2D COSY (500 MHz (CD$_3$)$_2$CO, 25 ºC) experiment of the cavitand 17io.

Figure S19: Selected region of $^3$P NMR spectra of the cavitand 17io
Figure S20: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 °C) of the cavitand 17io

Figure S21: HR-MS spectrum of 17io (left) and theoretical isotopic pattern (right).

4.6.2.- Characterization of 17oo:

$^1$H NMR (500 MHz, (CD$_3$)$_2$CO, 25 °C): δ (ppm) 8.38 (bs, 2H, NH$_a$), 8.29 (bs, 2H, NH$_b$), 7.41 (bs, 4H, H$_c$), 7.13 (d, $J_{H_b-H_d}$=8.0 Hz, 4H, H$_d$), 6.69 (bd, $J_{H_a-H_d}$=8.0 Hz, 4H, H$_e$), 6.03 (d, $J_{H_c-NH_a}$=2.6 Hz, 4H, H$_f$), 5.98 (d, $J_{H_b-NH_b}$=2.6 Hz, 4H, H$_g$), 3.56 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$Cl), 2.51-2.23 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$Cl), 2.23-2.13 (m, 20H, P(OR)$_{20}$CH$_2$CH$_2$ (J$_{H_b-H_d}$=27.7 Hz)+ p-(CH$_3$)$_4$), 1.72 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$Cl), 1.48-1.11 (m, 14H, P(OR)$_{14}$CH$_2$CH$_2$CH$_2$CH$_2$Cl) + CH$_2$CH$_2$CH$_2$CH$_2$Cl).

$^{31}$P NMR (160 MHz (CDCl$_3$, 25 °C): δ (ppm) 28.4.

$^{13}$C NMR (400 MHz, (CD$_3$)$_2$CO, 25 °C): δ (ppm) 151.3, 151.2, 146.7, 138.4, 137.1, 131.2, 127.3, 127.3, 125.5, 120.8, 120.8, 106.0, 105.9, 49.00, 45.6, 40.1, 33.8, 23.2, 22.3, 20.8, 15.9, 7.2, 7.1.

HR-MS (HPLC-ESI-TOF) (C$_{68}$H$_{79}$Cl$_4$N$_4$O$_6$P$_2$) Meas. m/z = 1249.4196 [M+H]$^+$; m/z = 1249.4223.

Scheme S8: Molecular structure and proton assignment of the cavitand 17oo.
Figure S22: $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, 25 °C) of the cavitand 1700

Figure S23: 2D COSY (500 MHz (CD$_3$)$_2$CO, 25 °C) spectra of the cavitand 1700.
Figure S24: Depicted region of $^{31}$P NMR spectra of the cavitand 1700

Figure S25: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 °C) of the cavitand 1700

Figure S26: HR-MS spectrum of 1700 (left) and theoretical isotopic pattern (right).

4.6.3.- Characterization of 17ii:

$^1$H NMR (500 MHz, (CD$_3$)$_2$CO, 25 °C): $\delta$ (ppm) 9.13 (bs, 2H, NH$_a$), 8.22 (bs, 2H, NH$_b$), 7.17 (d, $J_{HH-dHe}=$7.8 Hz, 4H, $H_d$), 6.79 ($J_{Hd-He}=$7.8 Hz, 4H, $H_e$), 6.70 (bs, 4H, $H_f$), 6.07 (d, $J_{Hf-NH_a}=$2.9 Hz, 4H, $H_g$), 5.99 (d, $J_{Hg-NH_b}=$2.9 Hz, 4H, $H_g$). 3.56 (m, 8H, CH$_2$CH$_2$CH$_2$CH$_2$Cl), 2.53-2.22 (m, 24H, CH$_2$CH$_2$CH$_2$CH$_2$Cl +
P(O)\textsubscript{(in)}\textsubscript{CH\textsubscript{2}CH\textsubscript{3}} (\textit{J}_{\text{H-H}}=27.7 \text{ Hz}) + \textit{p-CH\textsubscript{3}H}, 1.74 (m, 8H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}Cl), 1.45-0.95 (m, 14H, CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}CH\textsubscript{2}Cl + P(O)\textsubscript{(in)}\textsubscript{CH\textsubscript{2}CH\textsubscript{3}} (\textit{J}_{\text{H-H}}=21.8 \text{ Hz})).

\textsuperscript{31}P NMR (160 MHz (CDCl\textsubscript{3}, 25 \degree C): \delta (ppm) 29.4.

\textbf{Scheme S9:} Molecular structure and proton assignment of the cavitand 17ii.

\textbf{Figure S27:} 'H NMR (500 MHz, (CD\textsubscript{3})\textsubscript{2}CO, 25 \degree C) of the cavitand 17ii
Figure S28: 2D COSY (500 MHz (CD$_3$)$_2$CO, 25 °C) spectra of the cavitand 17ii.

Figure S29: Selected region of $^3$P NMR spectra of the cavitand 17ii
4.7.- Synthesis and characterization of bis-methylene bridged cavitand 18

To an ace pressure tube equipped with a magnetic stir bar and plunger valve, the calix[4]pyrrole 16a was added (176 mg, 0.16 mmol) together with K₂CO₃ (177 mg, 1.28 mmol, 8 eq.). The system was dried under high vacuum for 3 hours. The vacuum was satisfied with argon and 16 mL of anhydrous DMSO were added. Then, the bromochloromethane (53.6 μL, 0.8 mmol, 5 eq.) was added in one portion. The reaction mixture was heated up to 100 °C for 1 h in an oil bath. The reaction mixture was then cooled down to room temperature and poured into 10% HCl. The resulting suspension was extracted three times with DCM. The organic extracts were combined, washed with water three times, dried over Na₂SO₄, filtered and evaporated under reduced pressure, yielding a pale yellow solid. The crude was purified by silica gel column chromatography using DCM:Hexane (95:5) as eluent. The desired fractions were concentrated under reduced pressure to obtain 21.5 mg of a colorless solid as a final product, 12% yield.

**Scheme S10:** Synthetic scheme for the preparation of cavitand 18. The molecular structure of the cavitand includes the proton assignment.

**¹H NMR (400 MHz, (CD₃)₂CO, 25 °C):** δ (ppm) 8.49 (bt, J_NHB-HH ~2.6 Hz, 2H, NH₁), 8.30 (bt, J_NHB-HH ~2.6 Hz, 2H, NH₂), 7.00 (bd, J_NHB-HH ~7.8 Hz, 4H, H₁), 6.79 (bd, J_NHB-HH ~1.4 Hz, 4H, H₂), 6.52 (d, J_NHB-HH ~8.3 Hz, 2H, H₃), 6.51 (dd, J_NHB-HH ~7.8 Hz, J_NHB-HH ~1.4 Hz, 4H, H₄), 6.02 (d, J_NHB-HH ~2.6 Hz, 4H, H₅), 5.98 (d, J_NHB-HH ~2.6 Hz, 4H, H₆), 5.43 (d, J_NHB-HH ~8.3 Hz, 2H, H₇), 3.54 (m, 8H, CH₂CH₂CH₂PYCl), 2.60-2.16 (m, 8H, CH₂CH₂CH₂CH₂PYCl), 2.13 (s, 12H, p-(CH₃)), 1.72 (m, 8H, CH₂CH₂CH₂CH₂PYCl), 1.50-1.05 (m, 8H, CH₂CH₂CH₂CH₂PYCl).

**¹³C NMR (100 MHz, (CD₃)₂CO, 25 °C):** δ (ppm) 154.33, 145.44, 138.21, 136.04, 130.22, 126.05, 122.18, 104.92, 104.76, 48.27, 44.74, 39.39, 32.96, 22.43, 15.30.

**HR-MS (HPLC-ESI-TOF)** (C₃₆H₄1Cl₃N₄O₄) Meas. m/z = 1125.4359 [M+H]+; m/z = 1125.4380
Figure S30: $^1$H NMR (400 MHz, (CD$_3$)$_2$CO, 25 °C) of the cavitand 18

Figure S31: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 °C) of the compound 18
4.8. - Synthesis and characterization of water-soluble cavitand 1io

Scheme S11: Synthetic scheme for the preparation of cavitand 1io. The molecular structure of the cavitand shows the proton assignment.

To a Schlenk tube, the calix[4]pyrrole 17io (16.7 mg, 0.013 mmol) was dissolved in 2.5 mL of dry pyridine (distilled over CaH2) under argon atmosphere. Then, the reaction was heated up to 110 °C in an oil bath overnight. Next morning, yellow solids were observed. The reaction mixture was cooled down to room temperature and concentrated under reduced pressure. The obtained solid was triturated with DCM, filtered and washed with more DCM, acetone, and hexane. We finally obtained 19.3 mg of a yellow solid, 92% yield.

H NMR (500 MHz, D,O, 25 °C): δ (ppm) 8.63 (bm, 8H, Hb), 8.50 (bt, J_Hb-Hc~7.7 Hz, 4H, Hc), 7.95 (bm, 8H, Hb), 7.27 (bd, J_Hi-Hh~8.0 Hz, 2H, †Hh), 7.22 (bd, J_He-Hf~8.0 Hz, 2H, Hf), 6.84 (bm, 12H, Hg, †Hg), 6.70 (bs, 4H, Hf), 5.98 (bs, 2H, †Hd), 5.91 (bs, 2H, Hd), 5.81 (bm, 4H, †He + †Hf), 4.49 (bm, 8H, CH2CH2CH2CH2PyCl), 2.58-2.10 (bm, 24H, CH2CH2CH2CH2PyCl + Hg + †Hg + †Hh + †Hf (J_Hf-J_g~26.50 Hz)) 2.01-1.65 (bm, 8H, CH2CH2CH2CH2PyCl), 1.49-1.41 (2 x bdt, 4H, Hn + †Hn (J_Hn-J_g~22.30 Hz, J_Hn-J_f~7.8 Hz)) 1.20-0.82 (bm, 8H, CH2CH2CH2CH2PyCl).

P NMR (202 MHz, D2O, 25 °C): δ (ppm) 33.12, 33.09

HR-MS (HPLC-ESI-TOF) (C88H98N8O6P2) Meas. m/z = 356.1783 [M-4Cl]4+ ; m/z = 356.1766
Figure S33: $^1$H NMR (400 MHz, D$_2$O, 25 $^\circ$C) of the cavitand iio

Figure S34: $^{13}$C NMR (100 MHz, (CD$_3$)$_2$CO, 25 $^\circ$C) of the compound iio
Figure S35: Depicted region of the 31P NMR (202 MHz, D2O, 25 °C) spectra of the compound 110.

Figure S36: HR-MS spectrum of 110 (left) and theoretical isotopic pattern (right).

4.9. Synthesis and characterization of water-soluble cavitand 100

Scheme S12: Synthetic scheme for the preparation of cavitand 100. The molecular structure of the cavitand shows the proton assignment.

To a Schlenk tube, the calixpyrrole 1700 (20.7 mg, 0.017 mmol) was dissolved in 2.8 mL of dry pyridine (distilled over CaH2) under argon atmosphere. Then the reaction was heated up to 110 °C in an oil bath overnight. Next morning, yellow solids were observed. The reaction mixture was cooled down at room temperature and concentrated under vacuum. The obtained solid was triturated with DCM, filtered and washed with DCM, acetone and hexane. We finally obtained 16.5 mg of a yellow solid, 64% yield.
$^1$H NMR (500 MHz, (D$_2$O, 25 °C): 8.59 (bm, 8H, $H_a$), 8.46 (bt, $J_{1b,1c}$=7.6 Hz, 4H, $H_c$) 7.90 (bm, 8H, $H_b$), 7.20 (bd, $J_{1a,1c}$=6Hz, 4H, $H_a$), 6.85 (bs, 4H, $H_d$), 6.77 (bm, 4H, $H_e$), 5.90 (bs, 4H, $H_d$), 5.82 (bs, 4H, $H_e$), 4.78 (bs, 8H, CH$_2$CH$_2$CH$_2$PyCl), 2.50-2.17 (bm, 20H, CH$_2$CH$_2$CH$_2$PyCl + Ho + Hm (+$J_{Hg-P}$=26.50 Hz)) 1.88 (bs, 8H, CH$_2$CH$_2$CH$_2$PyCl), 1.41 (bdt, 4H, $H_n$ (+$J_{Hg-P}$=22.30 Hz, $J_{Hg-Hn}$=7.8 Hz)) 1.04 (bm, 8H, CH$_2$CH$_2$CH$_2$PyCl).

$^{13}$C NMR (125 MHz, D$_2$O, 25 °C): δ (ppm) 148.67, 148.59, 145.28, 144.32, 143.76, 137.30, 130.44, 127.85, 127.21, 124.64, 124.54, 119.80, 104.09, 60.96, 47.82, 37.91, 30.12, 20.67, 20.50, 15.05, 5.92, 5.86.

$^{31}$P NMR (202 MHz, D$_2$O, 25 °C): δ (ppm) 33.12

HR-MS (HPLC-ESI-TOF) (C$_{88}$H$_{98}$ClN$_8$O$_6$P$_2$) Meas. m/z = 486.5598 [M-3Cl]$^+$; m/z = 486.5586.

Figure S37: $^1$H NMR (500 MHz, D$_2$O, 25 °C) of the compound 100

Figure S38: $^{13}$C NMR (125 MHz, D$_2$O, 25 °C) of the compound 100

Figure S39: Depicted region of the $^{31}$P NMR (202 MHz, D$_2$O, 25 °C) spectra of the compound 100
**Figure S40:** HR-MS spectrum of 100 (left) and theoretical isotopic pattern (right).

### 4.10. Synthesis and characterization of water-soluble cavitand 2

![Scheme S13](image)

**Scheme S13:** Synthetic scheme for the preparation of cavitand 2. The molecular structure of the cavitand shows the proton assignment.

To a Schlenk tube, the calixpyrrole 18 (20 mg, 0.018 mmol) was dissolved in 3 mL of dry pyridine (distilled over CaH₂) under argon atmosphere. Then the reaction was heated up to 110 °C in an oil bath overnight. Next morning, yellow solids were observed. The reaction mixture was cooled down to room temperature and concentrated under vacuum. We finally obtained 16.5 mg of a yellow solid, 64% yield.

**1H NMR** (400 MHz, (D₂O, 25 °C): δ (ppm) 8.60 (bd, J₁₆₋₁₇=5.3 Hz, 8H, H₄), 8.47 (bt, J₁₅₋₁₆=7.0 Hz, 4H, H₅) 7.93 (bm, 8H, H₆), 7.15 (bd, J₁₄₋₁₅=5.3 Hz, 4H, H₇), 6.64 (bm, 8H, H₈ + H₉), 5.92 (bs, 4H, H₁₀), 5.86 (bs, 4H, H₁₁), 5.45 (bd, J₁₂₋₁₃=5.3 Hz, 2H, H₁₂), 4.47 (bm, 8H, CH₂CH₃CH₂CH₂PyCl), 2.40-2.15 (bm, 20H, CH₂CH₂CH₃CH₂PyCl + p-(CH₃)₂) 1.84 (bs, 8H, CH₂CH₂CH₂CH₂PyCl), 1.16-0.87 (bm, 8H, CH₂CH₂CH₂CH₂PyCl).

**13C NMR** (125 MHz, D₂O, 25 °C): δ (ppm) 154.0, 145.4, 143.8, 137.8, 136.9, 130.4, 127.9, 122.9, 105.1, 104.1, 61.3, 48.0, 37.4, 30.4, 20.8, 15.3.

**HR-MS** (HPLC-ESI-TOF) (C₈₆H₉₂N₈O₄Cl) Meas. m/z = 445.2314 [M-3Cl]⁺; m/z = 445.2305.

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S28
Figure S41: $^1$H NMR (400 MHz, (D$_2$O, 25 °C) of the compound 2

Figure S42: $^{13}$C NMR (125 MHz, (CD$_3$)$_2$CO, 25 °C) of the compound 2.

Figure S43: HR-MS spectrum of 2 (left) and theoretical isotopic pattern (right).
4.11. Synthesis and characterization of water-soluble receptor 3

Scheme S14: Synthetic scheme for the preparation of calix[4]pyrrole 3. The molecular structure of the receptor shows the proton assignment.

To a Schlenk tube, the aryl-extended calix[4]pyrrole 16b (66.7 mg, 0.064 mmol) was dissolved in 11 mL of dry pyridine (distilled over CaH₂) under argon atmosphere. Then the reaction was heated up to 110 °C in an oil bath overnight. Next morning, yellow solids were observed. The reaction mixture was cooled down to room temperature and concentrated under vacuum. The obtained solid was triturated with DCM, filtered and washed with more DCM, acetone and hexane. We finally obtained 85.4 mg of a yellow solid, 98% yield.

1H NMR (400 MHz, D₂O, 25 °C): 8.60 (bd, J_{H_a-H_c}~5.8 Hz, 8H, H_a), 8.49 (bt, J_{H_b-H_c}~7.5 Hz, 4H, H_b) 7.95 (bm, 8H, H_c), 7.13 (bd, J_{H_d-H_e}~8.3 Hz, 8H, H_d), 6.82 (bd, J_{H_e-H_d}~8.3 Hz, 4H, H_e), 5.85 (bs, 8H, H_f), 4.46 (bm, 8H, CH₂CH₂CH₂CH₂PyCl), 2.39-2.26 (bm, 20H, CH₂CH₂CH₂CH₂PyCl + p-CH₃), 1.82 (bm, 8H, CH₂CH₂CH₂CH₂PyCl). 13C NMR (125 MHz, D₂O, 25 °C): δ (ppm) 145.5, 143.8, 141.5, 137.5, 136.7, 128.3, 128.0, 104.5, 61.1, 47.9, 38.7, 30.4, 20.8, 20.1

HR-MS (HPLC-ESI-TOF) (C₈₄H₉₂ClN₈) Meas. m/z = 415.9032 [M-3Cl]⁺; m/z = 415.9039.

Figure S44: 1H NMR (400 MHz, D₂O, 25 °C) of 3
Figure S45: $^{13}$C NMR (125 MHz, (CD$_3$)$_2$CO, 25 °C) of 3

Figure S46: HR-MS spectrum of 3 (left) and theoretical isotopic pattern (right)
5. NMR titration experiments in D$_2$O

The $^1$H NMR titration experiments were carried out on a Bruker Avance 400 MHz, at room temperature in deuterated water. For those cases in which the binding constant values were $K_a \geq 10^4$ M$^{-1}$, and/or the chemical exchange between free and bound counterparts was slow on the NMR time scale, the quantification of the binding constant was assessed by ITC experiments (see section below). The association constant values between receptors 100, 10, 2, and 3 were determined by monitoring the chemical shift changes experienced by the receptor's proton signals as incremental amounts of the different guests (7, 8, and 9) were added. The values of the association constants, $K_a$, were determined by fitting the chemical shift changes to a 1:1 binding model using HypNMR2008 software.$^{4,5}$

5.1. Receptor 100

5.1.1. 100 vs β-lactam 4

Figure S47: Selected regions of the $^1$H NMR spectra recorded during the titration of 100 (1.01 mM) with incremental amounts of 4 in D$_2$O. a) free 100; b) 0.5 eq of 4; c) 1.5 eq of 4, d) 2.0 eq of 4; e) 3.0 eq of 4, and f) free 4.
5.1.2. 100 vs γ-lactam 5

Figure S48: Selected regions of the 'H NMR spectra recorded during the titration of 100 (1.02 mM) with incremental amounts of 5 in D₂O. a) free 100; b) 0.6 eq of 5; c) 1.1 eq of 5, d) 1.6 eq of 5; e) 2.2 eq of 5, and f) free 5. Prime labels represent the proton signals of 5 included in the receptor’s cavity.
Figure S49: Selected region of the ROESY $^1$H NMR spectra of the complex 5⊂100 in presence of 2.2 eq 5. Primed letters represent the proton signals of 5 included in the receptor's cavity.
5.1.3. 100 vs δ-lactam 6

Figure S50: Selected regions of the 'H NMR spectra recorded during the titration of 100 (1.04 mM) with incremental amounts of 6 in D₂O. a) free 100; b) 0.5 eq of 6; c) 1.0 eq of 6; d) 1.4 eq of 6; e) 1.9 eq of 6, and f) free 6. Primed letters represent the proton signals of 6 included in the receptor’s cavity.
**Figure S51**: Selected region of ROESY $^1$H NMR spectra of the complex 6⊂100 in presence of 1.9 eq 6. Primed letters represent the proton signals of 6 included in the receptor’s cavity.
5.1.4. 100 vs ω-lactam 7

Figure S52: Selected regions of the 1H NMR spectra recorded during the titration of 100 (1.05 mM) with incremental amounts of ω-lactam 7 in D2O. a) free 100; b) 0.45 eq of 7; c) 0.89 eq of 7; d) 1.32 eq of 7; e) 1.75 eq of 7; f) 2.17 eq of 7; g) 3.20 eq of 7; h) 4.18 eq of 7; i) 5.13 eq of 7; j) 6.93 eq of 7; k) 8.61 eq of 7, and l) free 7. Primed letters represent the proton signals of 100 in the complex.
**Figure S53:** Data analysis for $^1$H NMR titration of cavitand 100 with ω-lactam 7 (see Figure S52). Plot of observed and predicted changes in proton chemical shifts (ppm) of Hf, Hg, and Hs against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 807 \text{ M}^{-1}$.

**Figure S54:** Species distribution resulting from the analysis of the NMR binding study of receptor 100 with ω-lactam 7 (see above)
5.1.5. - 100 vs N-methyl γ-lactam 8

Figure S55: Selected regions of the "H NMR spectra recorded during the titration of 100 (1.04 mM) with incremental amounts of 8 in D₂O. a) free 100; b) 0.5 eq of 8; c) 1.0 eq of 8; d) 1.4 eq of 8; e) 2.4 eq of 8; f) 3.5 eq of 8; g) 5.5 eq of 8; h) 7.3 eq of 8, and i) free 8. Primed letters represent the proton signals of 100 in the complex.
Figure S56: Data analysis for $^1$H NMR titration of cavitand 100 with guest 8 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of Hf, Hg, and Hh against total guest concentration (M) using a host:guest 1:1 theoretical binding model with $K_a = 474 \text{ M}^{-1}$.

Figure S57: Species distribution resulting from the analysis of the NMR binding study of receptor 100 with guest 8 (see above).
5.1.6. 100 vs Cyclohexanone 9

Figure S58: Selected regions of the ¹H NMR spectra recorded during the titration of 100 (1.02 mM) with incremental amounts of 9 in D₂O. a) free 100; b) 0.5 eq of 9; c) 1.1 eq of 9, d) 2.1 eq of 9; e) 4.1 eq of 9; f) 6.0 eq of 9; g) 7.6 eq of 9, and h) free 9. Primed letters correspond to the proton signals of 100 in the complex.
Figure S59: Data analysis for 1H NMR titration of cavitand 100 with guest 9 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of Hf, Hg, and Hs against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 1125$ M$^{-1}$.

Figure S60: Species distribution resulting from the analysis of the NMR binding study of receptor 100 with guest 9 (see above)
5.1.7. 100 vs δ-lactone 10

Figure S61: Selected regions of the 1H NMR spectra recorded during the titration of 100 (0.98 mM) with incremental amounts of 10 in D₂O. a) free 100; b) 0.5 eq of 10; c) 1.0 eq of 10; d) 1.5 eq of 10; e) 2.6 eq of 10, and f) free 10.
5.1.8. 100 vs cyclic urea 11

Figure S62: Selected regions of the $^1$H NMR spectra recorded during the titration of 100 (0.99 mM) with incremental amounts of 11 in D$_2$O. a) Free 100; b) 0.6 eq of 11; c) 1.2 eq of 11; d) 1.8 eq of 11, and e) free 11. Primed letters correspond to the proton signals of 9 included in the receptor’s cavity.
Figure S63: Selected region of the ROESY 1H NMR spectrum of the complex 11C100 prepared by adding 1.8 eq of 11 to 100. Primed letters correspond to the proton signals of 11 included in the receptor’s cavity.
3.1.9. 100 vs Pyridine N-oxide 12

Figure S64: Selected regions of the $^1$H NMR spectra recorded during the titration of 100 (1.03 mM) with incremental amounts of 12 in D$_2$O. a) Free 100; b) 0.5 eq of 12; c) 1.0 eq of 12; d) 1.6 eq of 12, and e) free 12. Primed letters correspond to the proton signals of 12 included in the receptor’s cavity.
Figure S65: Selected region of ROESY $^1$H NMR spectrum of the complex 12⊂100 in prepared by adding 1.6 eq of 12 to the solution of 100. Primed letters correspond to the proton signals of 12 included in the receptor's cavity.
5.2. - Receptor 1io

5.2.1. - 1io vs β-lactam 4

Figure S66: Selected regions of the 1H NMR spectra recorded during the titration of 1io (0.99 mM) with incremental amounts of 4 in D2O. a) Free 1io; b) 0.5 eq of 4; c) 1.0 eq of 4; d) 1.5 eq of 4; e) 2.8 eq of 4; f) 5.6 eq of 4 and g) free 4.
5.2.2. 1io vs γ-lactam 5

![Diagram of 1io and γ-lactam 5]

Figure S67: Selected regions of the $^1$H NMR spectra recorded during the titration of 1io (1.04 mM) with incremental amounts of 5 in D$_2$O. a) free 1io; b) 0.5 eq of 5; c) 1.0 eq of 5; d) 1.6 eq of 5; e) 2.3 eq of 5; and f) free 5. Primed letters correspond to the proton signals of 5 included in the receptor's cavity.
Figure S68: Selected region of ROESY $^1$H NMR spectrum of the complex $5 \subset 1io$ prepared by adding 2.3 eq of 5 to a solution of 1io. Primed letters correspond to the proton signals of 5 included in the receptor's cavity.
5.2.3. 1io vs δ-lactam 6

Figure S69: Selected regions of the 'H NMR spectra recorded during the titration of 1io (0.98 mM) with incremental amounts of 6 in D$_2$O. a) free 1io; b) 0.6 eq of 6; c) 1.1 eq of 6; d) 1.6 eq of 6; e) 2.7 eq of 6; and f) free 6. Prime labels represent the proton signals of 6 included in the receptor's cavity.
Figure S70: Selected region of ROESY $^1$H NMR spectrum of the complex 6cio prepared by adding 2.7 eq of 6 to a solution of rio. Primed letters correspond to the proton signals of 6 included in the receptor's cavity.
5.2.4. 1io vs ω-lactam 7

Figure S71: Selected regions of the $^1$H NMR spectra recorded during the titration of 1io (1.04 mM) with incremental amounts of ω-lactam 7 in D$_2$O. a) free 1io; b) 0.55 eq of 7; c) 1.09 eq of 7; d) 2.40 eq of 7; e) 3.67 eq of 7; f) 6.29 eq of 7; g) 9.02 eq of 7; h) 13.84 eq of 7, and i) free 7.
Figure S72: Data analysis for ‘H NMR titration of cavitand sio with ω-lactam 7 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of Hf, Hf, and (He + He) against total guest concentration (M), using a host-guest 1:1 theoretical binding model with $K_a = 106 \text{ M}^{-1}$.

Figure S73: Species distribution resulting from the analysis of the NMR binding study of receptor sio with ω-lactam 7 (see above).
5.2.5. 1io vs N-methyl γ-lactam 8

Figure S74: Selected regions of the $^1$H NMR spectra recorded during the titration of 1io (1.09 mM) with incremental amounts of 8 in D$_2$O. a) free 1io; b) 2.23 eq of 8; c) 5.72 eq of 8; d) 13.12 eq of 8; e) 16.51 eq of 8; f) 22.51 eq of 8; g) 27.68 eq of 8, and h) free 8.
**Figure S75:** Data analysis for $^1$H NMR titration of cavitand 1io with 8 (see above). Plot of the observed and predicted changes in protons chemical shifts (ppm) of Hf\(^\dagger\), Hf, and (He + Hf\(^\dagger\)) against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 31$ M\(^{-1}\).

**Figure S76:** Species distribution resulting from analysis of the NMR binding study of receptor 1io with 8 (see above).
5.3.- Receptor 2

5.3.1.- 2 vs β-lactam 4

Figure S77: Selected regions of the $^1$H NMR spectra recorded during the titration of 2 (1.03 mM) with incremental amounts of 4 in D$_2$O. a) Free 2; b) 0.6 eq of 4; c) 1.1 eq of 4; d) 2.3 eq of 4; e) 3.3 eq of 4, and f) free 4. Primed letters correspond to the proton signals of 4 included in the receptor's cavity.
Figure S78: Selected region of ROESY 'H NMR spectrum of the complex 4⊂2 prepared by adding 3.3 eq of 4 to a solution of 2. Primed letters correspond to the proton signals of 4 included in the receptor's cavity.
5.3.2. - 2 vs γ-lactam 5

Figure S79: Selected regions of the 1H NMR spectra recorded during the titration of 2 (0.98 mM) with incremental amounts of 5 in D₂O. a) free 2; b) 0.5 eq of 5; c) 1.0 eq of 5; d) 1.5 eq of 5; e) 2.8 eq of 5; and f) free 5. Primed letters correspond to the proton signals of 5 included in the receptor's cavity.
Figure S80: Selected region of ROESY 'H NMR spectrum of the complex 5⊂2 prepared by adding 2.8 eq of 5 to a solution of 2. Primed letters correspond to the proton signals of 5 included in the receptor’s cavity.
5.3.3. - 2 vs δ-lactam 6

Figure S81: Selected regions of the ¹H NMR spectra recorded during the titration of 2 (1.03 mM) with incremental amounts of 6 in D₂O. a) free 2; b) 0.6 eq of 6; c) 1.1 eq of 5; d) 1.6 eq of 6; e) 2.5 eq of 6; and f) free 6. Primed letters correspond to the proton signals of 6 included in the receptor's cavity.
**Figure S82**: Selected region of ROESY $^1$H NMR spectrum of the complex 6⊂2 prepared by adding 2.5 eq of 6 to a solution of 2. Primed letters correspond to the proton signals of 6 included in the receptor's cavity.
5.3.4. 2 vs \( \omega \)-lactam 7

Figure S83: Selected regions of the \(^1\)H NMR spectra recorded during the titration of 2 (1.09 mM) with incremental amounts of 7 in D$_2$O. a) free 2; b) 1.82 eq of 7; c) 3.58 eq of 7, d) 5.26 eq of 7; e) 8.46 eq of 7; f) 15.50 eq of 7, and g) free 7.
**Figure S84:** Data analysis for ¹H NMR titration of cavitand 2 with ω-lactam 7 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of H₆, H₇, and H₈ against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 211 \text{ M}^{-1}$.

**Figure S85:** Species distribution resulting from analysis of the NMR binding study of receptor 2 with ω-lactam 7 (see above).
5.3.5. 2 vs N-methyl γ-lactam 8

Figure S86: Selected regions of the 1H NMR spectra recorded during the titration of 2 (1.09 mM) with incremental amounts of 8 in D2O. a) free 2; b) 0.44 eq of 8; c) 0.87 eq of 8; d) 2.31 eq of 8; e) 3.31 eq of 8; f) 5.18 eq of 8; g) 6.92 eq of 8, and h) free 8.

Figure S87: Data analysis for 1H NMR titration of cavitand 2 with 8 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of Hα, Hε, and Hf against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 75$ M$^{-1}$. 
Figure S88: Species distribution resulting from analysis of the NMR binding study of receptor 2 with 8. (see above).
5.4. - Receptor 3

5.4.1. - 3 vs β-lactam 4

Figure S89: Selected regions of the 1H NMR spectra recorded during the titration of 3 (0.97 mM) with incremental amounts of 4 in D$_2$O. a) Free 3; b) 0.5 eq of 4; c) 1.1 eq of 4; d) 1.6 eq of 4; e) 2.6 eq of 4; f) 5.0 eq of 4; g) 7.2 eq of 4, and h) free 4.
5.4.2. 3 vs γ-lactam 5

Figure S90: Selected regions of the 1H NMR spectra recorded during the titration of 3 (0.98 mM) with incremental amounts of 5 in D2O. a) free 3; b) 0.6 eq of 5; c) 1.1 eq of 5; d) 1.5 eq of 5; e) 2.6 eq of 5; and f) free 5. Primed letters represent the proton signals of 5 included in the receptor’s cavity.
Figure S91: Selected region of ROESY $^1$H NMR spectrum of the complex $5\subset 3$ prepared by adding 2.6 eq of $5$ to a solution of $3$. Primed letters correspond to the proton signals of $5$ included in the receptor's cavity.
Figure S92: Selected regions of the $^1$H NMR spectra recorded during the titration of 3 (1.03 mM) with incremental amounts of 6 in D$_2$O. a) free 3; b) 0.5 eq of 6; c) 1.0 eq of 6; d) 1.6 eq of 6; e) 2.5 eq of 6; and f) free 6. Primed letters correspond to the proton signals of 6 included in the receptor’s cavity.
Figure S93: Selected region of ROESY $^1$H NMR spectrum of the complex 6⊂3 prepared by adding 2.5 eq of 6 to a solution of 3. Primed letters correspond to the proton signals of 6 included in the receptor’s cavity.
5.4.4. 3 vs ω-lactam 7

Figure S94: Selected regions of the $^1$H NMR spectra recorded during the titration of 3 (0.97 mM) with incremental amounts of 7 in D$_2$O. a) free 3; b) 0.54 eq of 7; c) 1.07 eq of 7; d) 1.59 eq of 7; e) 2.86 eq of 7; f) 4.08 eq of 7; g) 5.25 eq of 7; h) 7.48 eq of 7; i) 9.55 eq of 7; j) 14.15 eq of 7, and k) free 7.
Figure S95: Data analysis for \(^1\)H NMR titration of cavitand 3 with 7 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) of \(\text{H}_\text{d}, \text{H}_\text{e}, \text{anf} \text{H}_\text{f}\) against total guest concentration (M), using a host:guest 1:1 theoretical binding model with \(K_a = 544 \text{ M}^{-1}\).

Figure S96: Species distribution resulting from analysis of the NMR binding study of receptor 3 with 7 (see above).
Figure S97: Selected regions of the $^1$H NMR spectra recorded during the titration of 3 (1.09 mM) with incremental amounts of 8 in D$_2$O. 
a) free 3; b) 0.45 eq of 8; c) 0.89 eq of 8, d) 1.33 eq of 8; e) 2.39 eq of 8; f) 3.41 eq of 8; g) 4.40 eq of 8; h) 6.26 eq of 8; i) 7.99 eq of 8; j) 9.61 eq of 8, and h) free 8.
Figure S98: Data analysis for $^1$H NMR titration of cavitand 3 with 8 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) $\delta_{Hd}$, $\delta_{He}$, and $\delta_{Hf}$ against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 567 \text{ M}^{-1}$.

Figure S99: Species distribution resulting from analysis of the NMR binding study of receptor 3 with 8 (see above).
6.- Spectra of the 6\textsubscript{100} complex

6.1.- Solvent suppression experiments

Figure S100: 'H NMR spectra (400 MHz) in a 9:1 H\textsubscript{2}O:D\textsubscript{2}O solution mixture employing the W5 pulse sequence of a) free 100 and b) 6\textsubscript{100} (1 eq. added). Primed letters indicate the proton signals of 6 included in the cavity of 100. The NHs of the 100 receptor involved in hydrogen-bonding interactions with 6 are indicated with the dashed circle.
6.2.- ROESY ¹H NMR experiment of 6⊂100 complex

Figure S10: ROESY ¹H NMR spectrum (400 MHz) of the complex 6⊂100 prepared by adding 1.9 eq of 6 to a solution of 100. Primed letters indicate the proton signals of 6 and 100 in the complex. Cross peaks due to intermolecular close-contacts are indicated with arrows.
7.- ¹H NMR titration experiments in CDCl₃

7.1.- 1700 vs cyclohexanone 9

Figure S102: Selected regions of the ¹H NMR spectra recorded during the titration of 1700 (0.99 mM) with incremental amounts of 9 in CDCl₃: a) free 1700; b) 1.0 eq of 9; c) 3.7 eq of 9, d) 11.9 eq of 9, and e) free 9.
Figure S103: Data analysis for $^1$H NMR titration of cavitand 1700 with 9 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) $H_a$, $H_d$, an $H_f$ against total guest concentration (M), using a host:guest 1:1 theoretical binding model with $K_a = 14.9 \text{ M}^{-1}$.

Figure S104: Species distribution resulting from analysis of the NMR binding study of receptor 1700 with 9 (see above).
7.2. 1700 vs γ-lactone 10

Figure S105: Selected regions of the 'H NMR spectra recorded during the titration of 1700 (1.03 mM) with incremental amounts of 10 in CDCl₃. a) free 1700; b) 0.9 eq of 10; c) 5.8 eq of 10, d) 12.0 eq of 10, and e) free 10.
**Figure S106:** Data analysis for the $^1$H NMR titration of cavitand 1700 with 10 (see above). Plot of observed and predicted changes in proton chemical shifts (ppm) $\text{H}_a$, $\text{H}_d$, and $\text{H}_f$ against total guest concentration (M), using a host:guest 1:1 theoretical binding model $K_a = 88.3 \text{ M}^{-1}$.

**Figure S107:** Species distribution resulting from analysis of the NMR binding study of receptor 1700 with 10 (see above).
8.- ITC experiments in Milli-Q water

Titrations were carried out on a Microcal VP-ITC microcalorimeter, at 298 K, in pure MilliQ water. The association constants between receptors 100, 10, 2, and 3 were determined by monitoring the heat released in response to the additions of incremental amounts of the different guests (4, 5, 6, 10, 11, and 12). The values of the association constant $K_a$ and the enthalpy of binding $\Delta H$ were calculated using the Origin 7 software package which uses least-squares minimization to obtain globally optimized parameters as described in Wiseman et al. In all cases the data fit was performed using a simple 1:1 binding model. The reported values of $K_a$, $\Delta G$, $\Delta H$, and $T\Delta S$ were determined by averaging the values of at least two titrations for each guest.

8.1.- Receptor 100

Figure S108: (Top) Raw data for the ITC titration in MilliQ water of receptor 100 towards a) β-lactam 4, b) γ-lactam 5, c) δ-lactam 6, d) δ-lactone 10, e) cyclic urea 11, and f) pyridine N-oxide 12. (Bottom) Normalized integration of heat vs molar ratio; the fit of the 1:1 theoretical binding isotherm (red line) to the experimental data is also shown. a) β-lactam $[4] = 20.732$ mM over $[100] = 3.026$ mM; b) γ-lactam $[5] = 4.505$ mM over $[100] = 0.633$ mM; c) δ-lactam $[6] = 10.842$ mM over $[100] = 1.528$ mM; d) δ-valerolactone $[10] = 9.053$ mM over $[100] = 0.842$ mM; e) cyclic urea $[11] = 2.553$ mM over $[100] = 0.373$ mM, and f) pyridine N-oxide $[12] = 2.100$ mM over $[100] = 0.303$ mM
Table S1: Thermodynamic constant values determined for the binding equilibria of cavitand 1oo with 4, 5, 6, 10, 11, and 12. All values represent the average of at least two ITC titration experiments. Errors (standard deviations) are determined to be less than 10%. [a] M⁺; [b] kcal/mol at 298 K.

8.2.- Receptor 1io

Figure S109: (Top) Raw data for the ITC titration in MilliQ water of receptor 1io towards a) β-lactam 4, b) γ-lactam 5, and c) δ-lactam 6. (Bottom) Normalized integration of heat vs molar ratio; the fit of the 1:1 theoretical binding isotherm (red line) to the experimental data is also shown. a) β-lactam [4] = 15.802 mM over [1io] = 1.466 mM; b) γ-lactam [5] = 11.302 mM over [1io] = 1.518 mM, and c) δ-lactam [6] = 11.803 mM over [1io] = 1.520 mM.

Table S2: Thermodynamic constant values determined for the binding equilibria of cavitand 1oo with 4, 5, and 6. All values represent the average of at least two ITC titration experiments. Errors (standard deviations) are determined to be less than 10%. [a] M⁺; [b] kcal/mol at 298 K.

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8.3. Receptor 2

Figure S110: (Top) Raw data for the ITC titration in MilliQ water of receptor 2 towards a) β-lactam 4, b) γ-lactam 5, and c) δ-lactam 6. (Bottom) Normalized integration of heat vs molar ratio; the fit of the 1:1 theoretical binding isotherm (red line) to the experimental data is also shown. a) β-lactam [4] = 8.106 mM over [2] = 0.999 mM; b) γ-lactam [5] = 10.753 mM over [2] = 1.499 mM, and c) δ-lactam [6] = 3.429 mM over [2] = 0.315 mM.

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Table S3: Thermodynamic constant values determined for the binding equilibria of cavitand 2 with 4, 5, and 6. All values represent the average of at least two ITC titration experiments. Errors (standard deviations) are determined to be less than 10%. [a] M⁻¹; [b] kcal/mol at 298 K.

8.4. Receptor 3

Figure S111: (Top) Raw data for the ITC titration in MilliQ water of receptor 3 towards a) β-lactam 4, b) γ-lactam 5, and c) δ-lactam 6. (Bottom) Normalized integration of heat vs molar ratio; the fit of the 1:1 theoretical binding isotherm (red line) to the experimental data is also shown. a) β-lactam [4] = 20.886

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Table S4: Thermodynamic constant values determined for the binding equilibria of cavitand 3 with 4, 5, and 6. All values represent the average of at least two ITC titration experiments. Errors (standard deviations) are determined to be less than 10%. [a] M⁻¹; [b] kcal/mol at 298 K.

9.- ITC experiments in CHCl₃ solution

9.1.- Receptor 1700

![Figure S112:](image) (Top) Raw data for the ITC titration in CHCl₃ of receptor 1700 towards a) δ-lactam 6, b) cyclic urea 11, and pyridine N-oxide 12. (Bottom) Normalized integration of heat vs molar ratio; the fit of the 1:1 theoretical binding isotherm (red line) to the experimental data is also shown. a) δ-lactam [6] = 3.936 mM over [1700] = 0.589 mM; b) cyclic urea [11] = 2.109 mM over [1700] = 0.294 mM, and c) pyridine N-oxide [12] = 2.100 mM over [1700] = 0.726 mM.

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Table S5: Thermodynamic constant values determined for the binding equilibria of cavitand 1700 with 6, 11, and 12. All values represent the average of at least two ITC titration experiments. Errors (standard deviations) are determined to be less than 10%. [a] M⁻¹; [b] kcal/mol at 298 K.
10.- References