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ARTICLE

A molecular receptor selective for zwitterionic alanine

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A molecular receptor has been synthesized joining an aza-crown ether with a chiral chromane which mimics the oxyanion hole of the enzymes. With this receptor an apolar host-guest complex with zwitterionic alanine has been achieved through the formation of up to seven H-bonds. This complex allows the extraction of aqueous alanine to a chloroform phase, while other natural amino acids are poorly extracted or are not extracted at all. Due to the chiral nature of the receptor, enantioselective extraction from the aqueous alanine solution to a chlorform phase takes place. X-Ray analysis combined with anisotropic effects, NOE and CD studies revealed the absolute configuration of both strong and weak complexes. Modelling studies also support the proposed structures. The presence of an oxyanion-hole motif in this structure was corroborated by X-ray diffraction studies.

Introduction

Amino acids are scientifically and technically important compounds. Despite being small molecules, they are essential in nature as building blocks of biological molecules and as a source for chirality and molecular recognition.[1] They are also attractive guests,[2] since they are able to experience many H-bonds due to the large functional group density they exhibit. Natural amino acids in its zwitterionic state are highly polar compounds. Hydrogen-bonds formation strongly stabilizes the charges in the amino acid groups, yielding good water solubility. On the contrary, they show a low solubility in organic solvents, which lack H-bond donor abilities. Therefore, the association of amino acids in a low polarity organic solvent is a challenging issue. Accordingly, most of the enantioselective receptors for amino acids found in the literature associate amino acid derivatives and not the natural zwitterionic amino acid. Nevertheless, the literature shows many ingenious receptors for amino acids in natural products supramolecular chemistry[3] and in water-soluble receptors.[4] Our group has also been successful in the preparation of several receptors for both zwitterionic amino acids and their derivatives.[5]

The three-point interaction model[6] implies that chiral recognition requires establishment of at least three non-equivalent interactions between the two molecules involved. In the case of zwitterionic amino acids, the carboxylate group provides the first binding site.[7] The recognition of the ammonium function provides the second anchoring point to the receptor. Crown ethers have been extensively used for their ability to bind ammonium cations and many synthetic receptors capable of associating amino acids in organic apolar solvents incorporate such ethers combined with H-bond donors.[8,9] The third point may come from a steric interaction due to the amino acid side chain.[8a,8b,8m]

In this paper, a chromane fragment including different substituents capable of forming H-bonds (figure 1) is linked with an aza-18-crown-6 ether to provide a molecular receptor **1**, which forms an oxyanion hole for the association of zwitterionic amino acids and a small cavity suitable to be filled with the methyl group of an alanine side chain.

Despite being a non-essential amino acid, alanine is of great importance in the diet, since it can regulate the amount of glucose[10] in the blood.[11] *L*-alanine supplements are used in cases of hypoglycaemia to prevent the organism from suffering low blood sugar or insuline shocksand. Alanine supplements in the diet may also improve health.[12]

Results and discussion

The structure of receptor **1** is shown in figure 1. Modelling studies[13] suggest the formation of four H-bonds with the amino acid carboxylate group, while three more H-bonds stabilize the ammonium group inside the aza-crown ether cavity.

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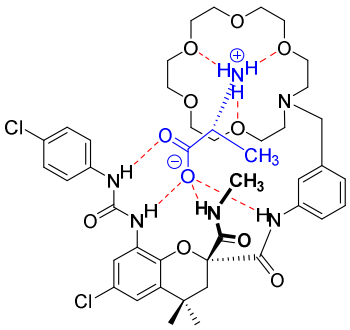
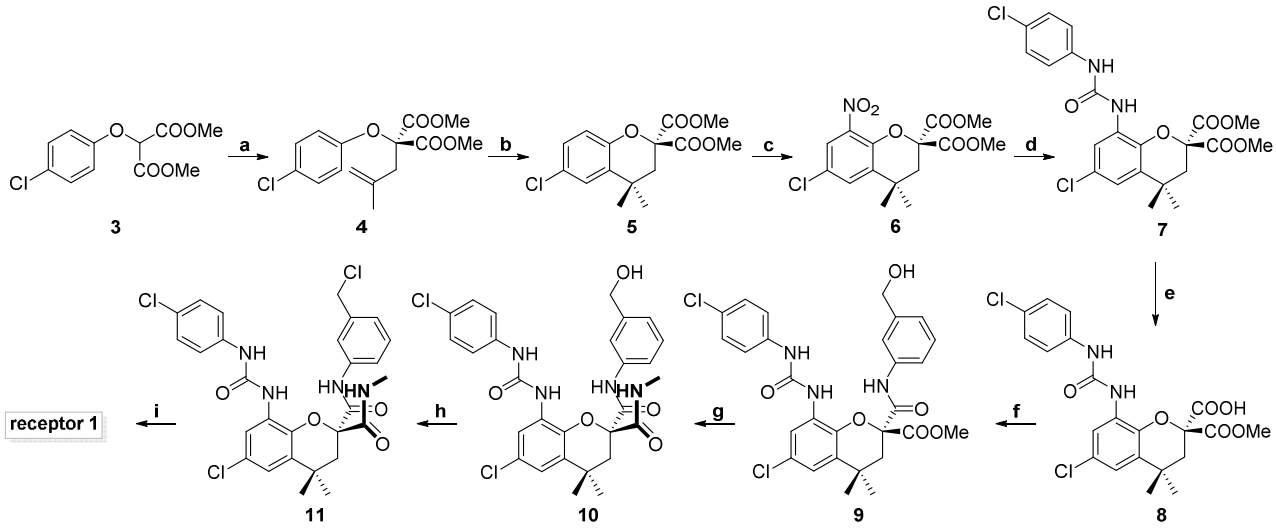


Figure 1. Structure of the associate of receptor **1** with zwitterionic alanine.

The preparation of receptor **1** was carried out from *p*-chlorophenol and dimethyl chloromalonate as shown in scheme 1. The phenoxymalonate **3** obtained from the reaction of these two compounds was then alkylated with chloroisobutene. The olefin, compound **4**, cyclizes with Eaton's reagent[14] to provide the chromane skeleton **5**.

Nitration, reduction and treatment of the resulting amine with chlorophenyl isocyanate yield the crucial H-bond donors of the urea moiety. Monohydrolysis of the malonate in compound **7** followed by coupling of the acid with 3-aminobenzyl alcohol using the anhydride method yield a benzyl alcohol (compound **9**), which undergoes aminolysis with methylamine.



Scheme 1. Preparation of receptor **1** [a) Na/MeOH, 3-chloro-2-methyl-1-propene; b) $MeSO_3H$, P_2O_5; c) HNO_3, CH_2Cl_2; d) 1) Zn, AcOH, 2) *p*-chlorophenyl isocyanate, CH_2Cl_2; e) LiOH, MeOH; f) DCC, (3-aminophenyl)methanol, $CHCl_3$; g) $MeNH_2$, MeOH; h) $SOCl_2$; i) 1-aza-18-crown-6, $CHCl_3$].

The resulting methylamide **10** experiences a significant change in the urea conformation, which can be detected in its ^{1}H NMR spectrum due to the strong shielding of the H-7 proton, which moves from 7.51 ppm in the ester **9** to only 6.49 ppm in the methylamide **10** (figure 2).

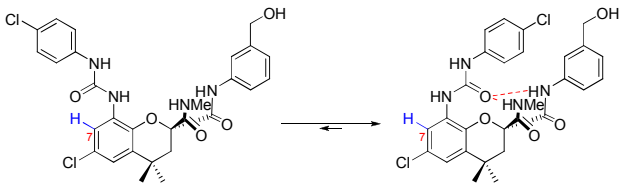


Figure 2. Conformational equilibrium in the methylamide **10**.

The benzyl alcohol, once transformed in the chloride with thionyl chloride, can be linked with the aza-crown ether to yield the expected receptor **1**. It has not been possible to crystalize the free receptor **1**. However, the purification of this compound can be easily achieved once dissolved in methanol after the addition of *L*-alanine.

The ^{1}H NMR spectrum of this mixture in deuterated methanol showed initially the splitting of the receptor **1** signals, due to the formation of two diastereomeric complexes. After a few minutes, the signals of both compounds disappeared due to its precipitation and only the impurities could be detected. After filtering, the crystals show a sharp melting point at 220°C. Nevertheless, the ^{1}H NMR spectrum in deuterated chloroform reveals the presence of the two diastereomeric complexes in a 1/1 ratio. In the spectrum of this mixture, all eight NHs show up as different signals, which we were able to assign with COSY and ROESY spectra (see ESI).

Crystallization from chloroform/methanol mixtures provided crystals suitable for X-ray analysis (figure 3).

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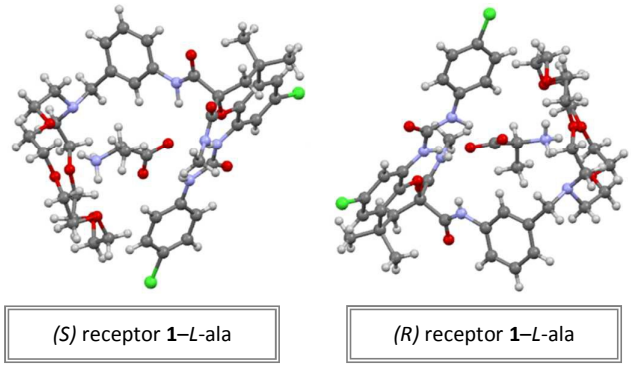

Figure 3. X ray structure of the quasi-racemate formed between racemic receptor **1** and *L*-alanine.

The structure obtained in the X-ray study showed the presence of both diastereomeric complexes in the crystal in a 1/1 ratio forming a quasi-racemate in which both enantiomers of the receptor **1** alternate. The *(S)* receptor **1** presents the *L*-alanine methyl group in a cavity formed by the crown ether and the aminophenylmethanol; on the other side, the *(R)* receptor **1** places the *L*-alanine methyl group close to the receptor **1** methylamine in an apparent *exo* position. A similar experiment carried out with *D,L*-alanine yielded crystals with a similar melting point (218°C), but in this case, the X-ray analysis (figure 4) shows the presence of two enantiomeric complexes, in which the *(S)* receptor **1** combines with *L*-alanine; while the *(R)* receptor **1** combines with *D*-alanine forming *"l"* complexes.

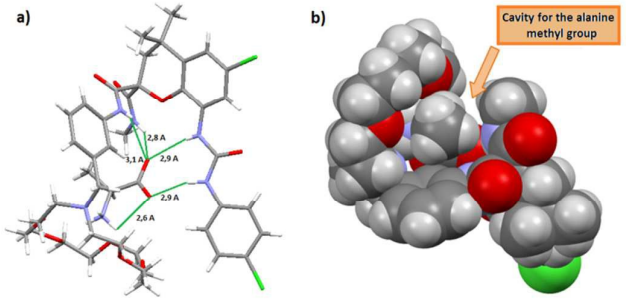

Figure 4. a) X-ray structure of the complex between racemic receptor **1** and racemic alanine (only the complex between the *(S)* receptor **1** and *L*-ala is shown for simplicity); b) space filling representation of receptor **1** showing the cavity generated for the association of alanine.

The crystallization of these two enantiomeric "*l*" complexes points to a certain degree of chiral discrimination, being the "*l*" complex more stable than the "*u*" complex. Indeed, dissolution of the previous crystals in deuterochloroform reveals the presence of two different sets of signals in the ^{1}H NMR spectrum for both receptor **1** and alanine, due to a slow breaking and forming complexes in the ^{1}H NMR time scale. These two sets of signals can be assigned to the two diastereomeric "*l*" and "*u*" complexes, being the intensity of the more stable "l" complex three times larger than that of the corresponding "*u*" type (see ESI). The different absorptions of the alanine methyl groups are in good agreement with the proposed structures, since this methyl group lies in the shielding cone of the aminomethylphenyl fragment in the "*l*" complex and is therefore shielded at 1.02 ppm, compared to the weak absorption of this methyl group in the "*u*" complex at 1.27 ppm. The ROESY spectrum of the strong complex shows a correlation of the alanine methyl group with one of the aromatic protons of the aminomethylphenyl fragment, showing the proximity of these groups in the associate. Meanwhile, in the weak complex a similar correlation is obtained between the alanine methyl group and the methylamide.

Crystallization of the racemic receptor **1** with glycine provides again crystals with a very similar melting point (221°C). The structure obtained by an X-ray analysis of these crystals is shown in figure 5, is very similar to the "*l*" strong complex with alanine. The H-bonds distances of 3.00 Å and 2.89 Å with the NHs of the urea moiety, 3.20 Å with the NH of the benzylamide and 2.80 Å with the NH of the methylamide are also similar in the alanine strong complex.

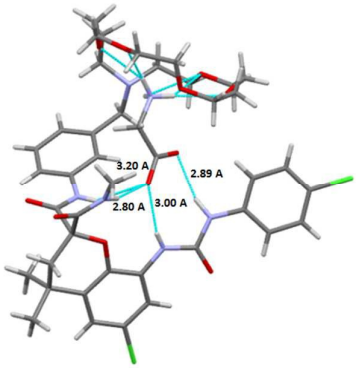

Figure 5. *X-ray structure of the complex between racemic receptor **1** and glycine.*

Since the structure of the weak "*u*" complex is different, with H-bonds distances of 2.87 Å and 2.96 Å with the NHs of the urea moiety, 2.94 Å with the NH of the phenylamide and 3.02 Å with the NH of the methylamide, there are probably steric interactions which reduce the stability of the "*u*" complex, due to collision between the alanine methyl group and the methylamide. Therefore, the cavity of receptor **1** seems to be ideally suited to host the alanine methyl group in the "*l*" geometry.

Amino acids with larger side chains are expected to undergo steric hindrance in their complexes and therefore, they should show a reduced stability. Attempts to crystallize receptor **1** with phenylalanine, leucine, valine and cysteine yielded only oily compounds.

Since it was not possible to crystallize a single enantiomer of receptor **1** using amino acids as guests, we tried to resolve the racemic mixture of receptor **1** with preparative TLC using chromatographic plates impregnated with *L*-alanine. This procedure has yielded good results for previous hosts.[15] Even if the surfaces of the "*l*" and "*u*" complexes of the racemic

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receptor **1** with *L*-alanine are very similar and, therefore, identical R_fs are expected, the fact that one complex is three times more stable than the other should help the separation. Indeed, the presence of the alanine in the TLC plates strongly increases the R_f of receptor **1**, when eluted with methylene chloride/isopronanol mixtures, yielding finally two different spots for the two diastereomeric complexes.

Scratching the silica of both spots and eluting it with a mixture of CH_2Cl_2/isopropanol yielded in both cases the complexes of receptor **1** with *L*-alanine.

Washing again the chloroform solution with water five times allows the isolation of the oily free receptor **1** enantiomers.

The CD spectra of these compounds confirm both the presence of two different enantiomers and their absolute configuration. Figure 6 shows the good agreement experimental CD spectra and the corresponding modeling studies (see details in ESI section).

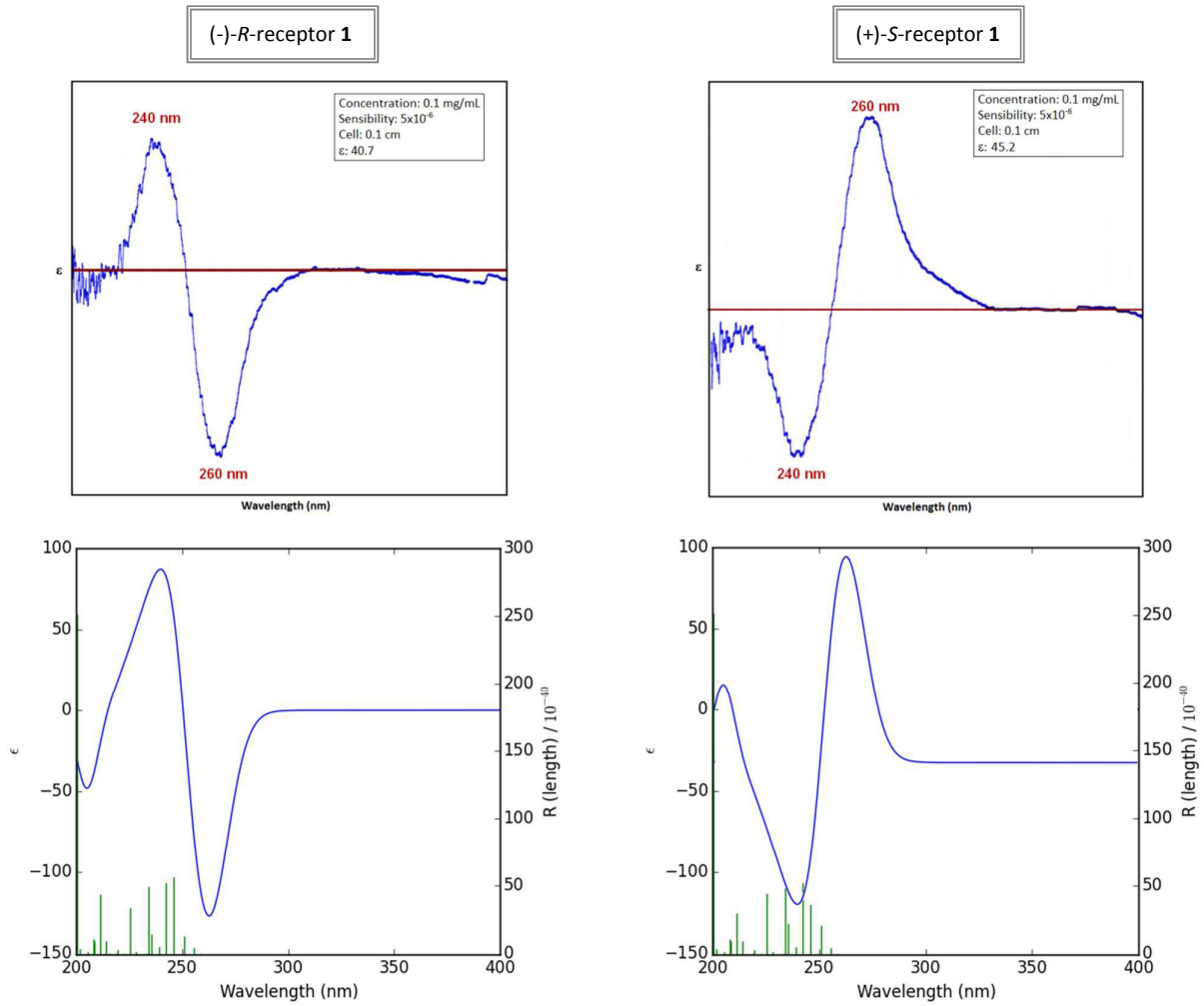

Figure 6. Experimental CD spectra of receptor **1** enantiomers (above; solvent: CH_2Cl_2; concentration: 0.1 mg/mL) and the corresponding calculated spectra (bellow).

The fit of the alanine methyl group within the cavity of the "*l*" associate suggested a good selectivity for this amino acid. A study was undertaken with aqueous saturated solutions of racemic alanine and other amino acids. Extraction with a 10^{-2}M chloroform solution of racemic receptor **1** allowed a direct assessment of the selectivity of the extraction, since the four possible complexes can be detected in the solutions and proton integration of the ^{1}H NMR spectra yielded the corresponding concentrations (table 1).

Polar amino acids like serine, aspartic acid, glutamic acid and tryptophan are not even extracted with receptor **1**. Nevertheless, more lipophilic amino acids like leucine (*entry 1*), cysteine (*entry 4*), phenylalanine (*entry 2*) and valine (*entry 3*) are also extracted to the chloroform solution in the presence of receptor **1**, although in all cases, there is a clear preference for alanine despite the fact that this amino acid is less lipophilic than the previous ones.

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Table 1. Chiral recognition of receptor **1** ($CDCl_3$, 20°C) and several amino acids (K_{rel}) and selectivity in the extraction of amino acids ($CDCl_3$ / H_2O, 20°C) compared to alanine with receptor **1** (R**1**-K_{sel}) and with receptor **2** (R**2**-K_{sel}). The last column shows the increased preference for the alanine complexation in the absence of the lipophilicity of the amino acid.

Entry	Amino acid	K_{rel}	R**1**-K_{sel}	R**2**-K_{sel}	R**1**-K_{sel}/R**2**-K_{sel}
1	Leucine	5.0	2.0	0.10	20
2	Phenylalanine	1.7	3.0	0.19	16
3	Valine	1.3	11.0	0.56	20
4	Cysteine	0.6	2.0	0.08	25

To illustrate the large preference that the cavity of receptor **1** shows for alanine, an additional study was carried out with a combination of 18-crown-6 ether and receptor **2** (figure 7), prepared from compound **7** by treatment with methylamine. A similar experiment as the previously described for receptor **1** under the same concentrations showed large preferences for the extraction of the most apolar amino acid (table 1). No chiral discriminations were detected with receptor **2** in the extraction of amino acids.

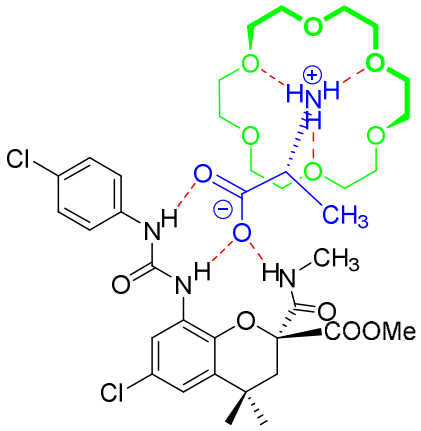

Figure 7. Structure of receptor **2** and the ternary complex formed with 18-crown- ether and alanine.

Conclusions

The racemic receptor **1** can be readily prepared from commercially available starting materials, linking a chromane, which acts as a multiple H-bond donor, with an aza-crown ether, that provides a suitable cavity for an ammonium group. This receptor shows an oxyanion hole observed in its X-ray structure and the presence of a complementary surface with alanine allowed the formation of an apolar host-guest complex by H-bond interactions. Due to this preference for alanine, this amino acid can be extracted exclusively from an aqueous solution in the presence of polar natural amino acids and selectively in the presence of lipophilic amino acids. Alanine also provides an easy way to resolve the racemic receptor mixture, making use of preparative TLCs impregnated in the amino acid. The structure of both diastereomeric complexes has been analysed by ^{1}H NMR, circular dichroism and modelling studies, showing steric hindrance as the main source for the receptor **1** selectivity.

Experimental

General experimental procedures

Solvents were purified by standard procedures and distilled before use. Reagents and starting materials obtained from commercial suppliers were used without further purification. IR spectra were recorded as neat film or in nujol and frequencies are given in cm^{-1}. Melting points are given in °C. NMR spectra were recorded on 200 MHz and 400 MHz spectrometers. ^{1}H NMR chemical shifts are reported in ppm with tetramethylsilane (TMS) as an internal standard. Data for ^{1}H are reported as follows: chemical shift (in ppm), number of hydrogen atoms, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br s = broad singlet) and coupling constant (in Hz). Splitting patterns that could not be clearly distinguished are designated as multiplets (m). Data for ^{13}C NMR are reported in ppm and hydrogen multiplicity is included. High-resolution mass spectral analyses (HRMS) were performed using ESI ionization and a quadrupole TOF mass analyzer. Column chromatographies were performed on 0.060-0.200 mm, 60 A silica gel.

Dimethyl 2-(4-chlorophenoxy)malonate (3). Commercial *p*-clorofenol (200 g, 1.56 mol) was treated with a KOH solution (103 g, 1.56 mol) in methanol (300 mL) and once it was all solved, methanol was eliminated under reduced pressure. The crude potassium salt thus obtained was solved in a mixture of bis(2-methoxyethyl) ether (500 mL) and toluene (200 mL) and the resulting mixture was distilled to remove water from the medium. Then, dimethyl chloromalonate (260 g, 1.56 mol) was added drop-wise from an addition funnel over the mixture obtained after the distillation described. Once the addition was completed, the reaction was worked up. Water and hexane were added to the mixture, the phases were separated and the organic one was steam distilled. The distillate was then cooled in an ice bath and filtered to recover the precipitate formed, corresponding to compound **3** (300 g, 75% yield), which can be purified by recrystallization with a $MeOH/CH_2Cl_2$ mixture. Mp 75–80 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 3.65 (6H, s), 5.19 (1H, s), 6.89 (2H, d, *J* = 9.0 Hz), 7.26 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 53.6 ($2CH_3$), 77.0 (CH), 117.0 (2CH), 128.1 (C), 129.9 (2CH), 155.5 (C), 165.9 (2C); IR (film) 750, 826, 1005, 1113, 1215, 1445, 1486, 1584, 1768, 1742, 2949 cm^{-1}; HRMS (ESI) Calcd for $C_{11}H_{11}O_5NaCl$ 281.0187, found 281.0193 $(M + Na)^+$.

Dimethyl 2-(4-chlorophenoxy)-2-(2-methylallyl)malonate (4). Sodium methoxide was prepared first solving the sodium (6.7 g, 0.29 mol) in absolute methanol (150 mL). Then, compound **3** (75 g, 0.29 mol) and 3-chloro-2-methyl-1-propene (31.6 mL, 0.29 mol) were consecutively added to the reaction mixture while it was heated in an oil bath at 80-90 °C. The resulting mixture was heated under vigorous stirring for an hour and then, it was cooled to room temperature, poured onto a 2M aqueous solution of HCl and extracted with hexane. The

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organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was eliminated under reduced pressure. Compound **4** (93 g, 100% yield) was isolated as a viscous light yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.76 (3H, s), 3.00 (2H, s), 3.75 (6H, s), 4.80 (1H, s), 4.90 (1H, s), 6.65 (2H, d, *J* = 9.0 Hz), 7.20 (2H, d, *J* = 9.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 23.8 (CH_3), 41.8 (CH_2), 53.3 ($2CH_3$), 86.1 (C), 116.1 (CH_2), 119.5 (2CH), 127.9 (C), 129.5 (2CH), 139.5 (C), 153.9 (C), 168.2 (2C); IR (film) 827, 911, 1073, 1225, 1441, 1495, 1594, 1751, 2949 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{18}O_5Cl$ 313.0837, found 313.0846 $(M + H)^+$, 335.0657 $(M + Na)^+$.

Dimethyl 6-chloro-4,4-dimethylchroman-2,2-dicarboxylate (5). Methanesulfonic acid (428 mL, 6.59 mol) was dried with P_2O_5 (130 g, 0.92 mol) and heating in an oil bath at 150 °C until all the P_2O_5 was dissolved. Then, the mixture was cooled to 60 °C and compound **4** (93 g, 0.29 mol) was added drop-wise from an addition funnel, keeping the temperature of the reaction mixture below 60 °C. Once the addition was completed, the mixture was slowly poured onto iced water and extracted with ethyl acetate. The organic phase was consecutively washed with an NH_3 aqueous solution until basic pH and with water. Then it was dried over anhydrous Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. Compound **5** (56 g, 62% yield) was isolated as a white solid. Mp 85–90 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.26 (6H, s), 2.46 (2H, s), 3.81 (6H, s), 6.96 (1H, d, *J* = 8.7 Hz), 7.10 (1H, dd, *J* = 2.5, 8.7 Hz), 7.18 (1H, d, *J* = 2.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 30.6 (C), 30.9 ($2CH_3$), 40.6 (CH_2), 53.6 ($2CH_3$), 80.5 (C), 119.1 (CH), 126.1 (CH), 127.0 (C), 127.9 (CH), 132.2 (C), 150.0 (C), 168.6 (2C); IR (film) 825, 1060, 1222, 1278, 1431, 1487, 1762, 2959 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{17}O_5NaCl$ 335.0657, found 335.0660 $(M + Na)^+$, 313.0863 $(M + H)^+$.

Dimethyl 6-chloro-4,4-dimethyl-8-nitrochroman-2,2-dicarboxylate (6). Fuming HNO_3 (1.526 g/mL) (5.3 mL, 128 mmol) was added onto a solution of compound **5** (10 g, 32 mmol) in CH_2Cl_2 (20 mL). Once the addition was completed, the reaction mixture was poured onto iced water and the phases were separated. The organic phase was then washed with water, dried over anhydrous Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure, which led to 8 g (70% yield) of compound **6**, as a deep yellow solid. Mp 108–112 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.30 (6H, s), 2.52 (2H, s), 3.82 (6H, s), 7.41 (1H, d, *J* = 2.6 Hz), 7.68 (1H, d, *J* = 2.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 30.7 ($2CH_3$), 31.3 (C), 40.3 (CH_2), 53.9 ($2CH_3$), 81.1 (C), 123.7 (CH), 126.5 (C), 130.5 (CH), 136.0 (C), 144.0 (C), 152.5 (C), 167.5 (2C); IR (film) 841, 1061, 1144, 1217, 1242, 1427, 1457, 1550, 1750, 2952, 3084 cm^{-1}; HRMS (ESI) Calcd for $C_{15}H_{16}NO_7NaCl$ 380.0507, found 380.0508 $(M + Na)^+$, 358.0690 $(M + H)^+$.

Dimethyl 6-chloro-8-(3-(4-chlorophenyl)ureido)-4,4-dimethylchroman-2,2-dicarboxylate (7). Compound **6** (8 g, 22.4 mmol) was slowly added, in portions, onto a suspension of Zn (10.9 g, 166.8 mmol) in acetic acid (36.5 mL), as the reaction occurs violently and is strongly exotermic. After the addition was completed, the reaction mixture was filtered to remove the solid mass of Zn and the filtrate was poured onto iced water and filtered again to recover the white solid which precipitates, that corresponds to the desired intermediate amine (7.3 g). This amine was then solved in CH_2Cl_2 (20 mL) and treated with *p*-chlorophenyl isocyanate (3.4 g, 22.4 mmol) and when all the solid was dissolved, the solvent was eliminated under reduced pressure to isolate compound **7** (8.1 g, 75% yield) as a white solid. Mp 190–195 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.21 (6H, s), 2.44 (2H, s), 3.78 (6H, s), 6.78 (1H, d, *J* = 2.3 Hz), 7.20 (2H, d, *J* = 8.8 Hz), 7.38 (2H, d, *J* = 8.8 Hz), 8.07 (1H, br s, NH), 8.16 (1H, d, *J* = 2.3 Hz), 8.47 (1H, br s, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 30.8 ($2CH_3$), 31.0 (C), 41.8 (CH_2), 54.1 ($2CH_3$), 81.0 (C), 117.5 (CH), 118.5 (CH), 120.2 (2CH), 122.2 (C), 124.0 (C), 127.7 (C), 129.1 (2CH), 130.1 (C), 131.9 (C), 138.1 (C), 167.5 (C), 168.8 (2C); IR (film) 671, 812, 1056, 1208, 1441, 1538, 1652, 1755, 3320 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{23}N_2O_6Cl_2$ 481.0928, found 481.0927 $(M + H)^+$, 503.0752 $(M + Na)^+$.

6-Chloro-8-(3-(4-chlorophenyl)ureido)-2-(methoxycarbonyl)-4,4-dimethylchroman-2-carboxylic acid (8). Compound **7** (8.1 g, 16.8 mmol) was suspended in methanol (64 mL), treated with $LiOH{\cdot}H_2O$ (0.7 g, 16.8 mmol) and heated in an oil bath at 80 °C under argon atmosphere until all the solid was dissolved. Then the solvent was eliminated under reduced pressure and the crude product obtained was solved in ethyl acetate and washed with a 2M aqueous solution of HCl. The resulting organic phase was dried over anhydrous Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. 6.2 g (79% yield) of compound **8** were isolated as a white solid. Mp 170–178 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ (ppm) 1.19 (3H, s), 1.25 (3H, s), 2.40 (1H, d, *J* = 13.0 Hz), 2.50 (1H, d, *J* = 13.0 Hz), 3.77 (3H, s), 6.78 (1H, d, *J* = 2.5 Hz), 7.19 (2H, d, *J* = 8.8 Hz), 7.37 (2H, d, *J* = 8.8 Hz), 8.13 (1H, d, *J* = 2.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 30.6 (C), 31.0 ($2CH_3$), 41.0 (CH_2), 53.6 (CH_3), 80.9 (C), 117.2 (CH), 118.6 (CH), 120.2 (2CH), 127.2 (C), 127.6 (C), 128.9 (2CH), 129.5 (C), 131.8 (C), 137.8 (C), 138.3 (C), 169.2 (2C), 169.7 (C); IR (film) 827, 1076, 1162, 1232, 1442, 1572, 1723, 1777, 2968 cm^{-1}; HRMS (ESI) Calcd for $C_{21}H_{20}N_2O_6NaCl_2$ 489.0591, found 489.0586 $(M + Na)^+$.

Methyl 6-chloro-8-(3-(4-chlorophenyl)ureido)-2-((3-(hydroxymethyl)phenyl)carbamoyl)-4,4-dimethylchroman-2-carboxylate (9). *N,N'*-dicyclohexylcarbodiimide (1.7 g, 8.2 mmol) was added to a solution of compound **8** (4.0 g, 8.6 mmol) in chloroform (100 mL). After 2 minutes of continuous stirring at room temperature, 3-aminobenzyl alcohol (1.0 g, 8.1 mmol) was added, following the progress of the reaction by registering ^{1}H NMR spectra of aliquots directly taken from the reaction medium. When the reaction was over, the crude product was dissolved in CH_2Cl_2 and purified by column chromatography (CH_2Cl_2/EtOAc 6:4 mixture as the eluent), isolating 3.9 g (79% yield) of compound **9** as a vitreous solid. RMN ^{1}H (200 MHz, $CDCl_3$) δ (ppm) 1.24 (3H, s), 1.30 (3H, s), 2.53 (2H, dd, *J* = 14.3 Hz), 3.76 (3H, s), 4.61 (2H, s), 6.96 (1H, d, *J* = 2.4 Hz), 7.03 (1H, d, *J* = 7.5 Hz), 7.11 (2H, d, *J* = 8.8 Hz), 7.19 (1H, t, *J* = 8.0 Hz), 7.23 (2H, d, *J* = 9.6 Hz), 7.48 (1H, d, *J* = 8.2 Hz), 7.56 (1H, s), 7.62 (1H, d, *J* = 2.4 Hz), 8.06 (1H, s), 8.11 (1H,

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s), 9.51 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 30.2 (C), 31.3 ($2CH_3$), 40.5 (CH_2), 64.5 (CH_2), 82.4 (C), 120.6 (2CH), 123.9 (2CH), 126.1 (CH), 127.9 (C), 128.3 (C), 128.8 (C), 129.1 (3CH), 129.3 (2CH), 133.3 (C), 137.5 (C), 137.7 (C), 137.9 (C), 142.1 (C), 151.9 (C), 166.1 (C), 169.8 (C); IR (film) 1123, 1541, 1606, 1670, 1730, 3299 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{27}N_3O_6NaCl_2$ 594.1169, found 594.1167 $(M + Na)^+$.

6-Chloro-8-(3-(4-chlorophenyl)ureido)-*N*-(3-(hydroxymethyl)phenyl)-*N*,4,4-trimethylchroman-2,2-dicarboxamide (10). Compound **9** (3.9 g, 6.8 mmol) was added onto a mixture of methylamine (2.0 mL, 40% aqueous solution) and methanol (5.0 mL). When the reaction was over (^{1}H NMR), the solvent was eliminated under reduced pressure, isolating 3.6 g (93% yield) of compound **10**, as a vitreous solid. RMN ^{1}H (200 MHz, $CDCl_3$) δ (ppm) 1.30 (3H, s), 1.34 (3H, s), 2.41 (1H, d, *J* = 13.9 Hz), 2.60 (1H, d, *J* = 13.9 Hz), 2.89 (3H, d, *J* = 4.7 Hz), 4.62 (2H, s), 6.49 (1H, d, *J* = 2.2 Hz), 7.03 (1H, d, *J* = 2.5 Hz), 7.03 (1H, d, *J* =7.5 Hz), 7.11 (2H, d, *J* = 8.8 Hz), 7.29 (1H, t, *J* = 7.4 Hz), 7.34 (2H, d, *J* = 8.9 Hz), 7.60 (1H, d, *J* = 12.4 Hz), 7.71 (1H, s), 8.30 (1H, s), 8.57 (1H, s), 10.7 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 27.2 (CH_3), 30.5 ($2CH_3$), 31.3 (C), 41.6 (CH_2), 65.0 (CH_2), 81.1 (C), 119.6 (CH), 120.4 (CH), 120.2 (2CH), 123.6 (CH), 124.1 (CH), 124.5 (CH), 126.4 (C), 126.8 (C), 127.6 (C), 129.0 (2CH), 129.3 (CH), 131.9 (C), 137.4 (C), 138.1 (C), 142.2 (C), 144.7 (C), 154.7 (C), 168.6 (C), 170.3 (C); IR (film): 1223, 1541, 1606, 1684, 3312 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{28}N_4O_5NaCl_2$ 593.1329, found 593.1325 $(M + Na)^+$, 571.1500 $(M + H)^+$.

6-Chloro-*N*-(3-(chloromethyl)phenyl)-8-(3-(4-chlorophenyl)ureido)-*N*,4,4-trimethylchroman-2,2-dicarboxamide (11). Compound **10** (3.6 g, 6.3 mmol) was dissolved in thionyl chloride (3.0 mL) and this latest compound was then eliminated under reduced pressure. The crude product thus obtained was purified by crystallization in CH_2Cl_2 and 2.8 g (75% yield) of compound **11** were isolated. Mp 184-185°C; RMN ^{1}H (200 MHz, $CDCl_3$) δ (ppm) 1.34 (3H, s), 1.40 (3H, s), 2.38 (1H, d, *J* = 13.0 Hz), 2.67 (1H, d, *J* = 13.0 Hz), 2.92 (3H, d, *J* = 4.6 Hz), 4.50 (2H, s), 6.35 (1H, d, *J* = 2.1 Hz), 7.04 (1H, d, *J* = 2.4 Hz), 7.16 (2H, d, *J* = 8.7 Hz), 7.24 (1H, d, *J* =9.1 Hz), 7.32 (1H, t, *J* = 8.0 Hz), 7.36 (2H, d, *J* = 8.8 Hz), 7.74 (1H, d, *J* = 12.9 Hz), 7.78 (1H, s), 8.32 (1H, s), 8.55 (1H, s), 11.95 (1H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm) 26.8 (CH_3), 30.4 (C), 31.4 ($2CH_3$), 43.0 (CH_2), 46.0 (CH_2), 81.4 (C), 120.2 (2CH), 120.7 (CH), 120.9 (CH), 122.3 (CH), 122.7 (CH), 125.5 (C), 126.7 (CH), 127.4 (C), 127.7 (C), 129.0 (2CH), 129.5 (CH), 132.4 (C), 137.5 (C), 137.8 (C), 138.6 (C), 142.3 (C), 154.3 (C), 168.0 (C), 170.1 (C); IR (film) 1236, 1554, 1586, 1670, 3182, 3331 cm^{-1}; HRMS (ESI) Calcd for $C_{28}H_{27}N_4O_4NaCl_3$ 611.0990, found 611.0996 $(M + Na)^+$.

***N*-(3-((1,4,7,10,13-Pentaoxa-16-azacyclooctadecan-16-yl)methyl)phenyl)-6-chloro-8-(3-(4-chlorophenyl)ureido)-*N*,4,4-trimethylchroman-2,2-dicarboxamide (receptor 1).** 1-Aza-18-crown-6 (1.2 g, 4.6 mmol) was added onto a solution of compound **11** (2.1 g, 3.6 mmol) in chloroform (20 mL). The resulting reaction mixture was heated for 3 h at 60 °C in an oil bath under continuous stirring and then it was washed with water. The phases were separated and the organic one was dried over anhydrous Na_2SO_4 and filtered and the solvent was eliminated under reduced pressure. 1.9 g of receptor **1** (64% yield) were isolated, as a vitreous solid. RMN ^{1}H (200 MHz, $CDCl_3$) δ (ppm) 1.33 (3H, s), 1.35 (3H, s), 2.51 (2H, s), 2.74 (4H, t, *J* = 5.6 Hz), 2.87 (3H, d, *J* = 4.6 Hz), 3.57-3.64 (20H, m), 3.65 (2H, s), 6.66 (1H, s), 7.02 (1H, d, *J* = 2.3 Hz), 7.13 (2H, d, *J* = 8.7 Hz), 7.14 (1H, d, *J* =8.0 Hz), 7.23 (1H, t, J = 7.7 Hz), 7.36 (2H, d, *J* = 8.7 Hz), 7.50 (1H, s), 7.62 (1H, d, *J* = 7.9 Hz), 8.37 (1H, s), 8.60 (1H, s), 8.76 (1H, s), 10.32 (1H, s); RMN ^{13}C (50 MHz, $CDCl_3$) δ (ppm) 26.8 (CH_3), 30.3 (CH_3), 30.4 (CH_3), 31.1 (C), 42.7 (CH_2), 53.9 ($2CH_2$), 59.8 (CH_2), 70.3 ($10CH_2$), 81.3 (C), 119.6 (CH), 120.0 (2CH), 121.2 (CH), 123.1 (CH), 124.0 (CH), 125.9 (CH), 126.1 (C), 126.8 (C), 127.2 (C), 128.6 (2CH), 128.8 (CH), 132.1 (C), 136.9 (C), 138.0 (C), 143.4 (C), 154.4 (2C), 167.8 (C), 169.9 (C); IR (film) 1125, 1236, 1313, 1495, 1541, 1599, 1697, 3306 cm^{-1}; HRMS (ESI) Calcd for $C_{40}H_{52}N_5O_9Cl_2$ 816.3137, found 816.3167 $(M + H)^+$.

Methyl 6-chloro-8-(3-(4-chlorophenyl)ureido)-4,4-dimethyl-2-(methylcarbamoyl)chroman-2-carboxylate (receptor 2). A solution of compound **7** (400 mg, 0.83 mmol) in CH_2Cl_2 (1 mL) was treated with an excess of methylamine (290 μL, 3.32 mmol, 40% aqueous solution) and the resulting mixture was stirred at room temperature for 10 minutes. Then the solvent was eliminated under reduced pressure and the crude product thus obtained was purified by column chromatography (9:1 CH_2Cl_2/EtAcO mixture as eluent), isolating 210 mg (53 % yield) of the desired compound, receptor **2**, as a vitreous solid. RMN ^{1}H (400 MHz, $CDCl_3$) δ (ppm) 1.22 (3H, s), 1.27 (3H, s), 2.28 (1H, d, *J* = 14.3 Hz), 2.65 (1H, d, *J* = 14.3 Hz), 2.85 (3H, d, *J* = 4.7 Hz), 3.80 (3H, s), 6.88 (1H, d, *J* = 2.5 Hz), 7.02 (1H, br s), 7.24 (2H, d, *J* = 9.0 Hz), 7.38 (2H, d, *J* = 9.0 Hz), 7.93 (1H, br s), 8.05 (1H, d, *J* = 2.5 Hz), 8.07 (1H, br s); RMN ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 26.8 (CH_3), 30.0 (CH_3), 30.2 (CH_3), 31.1 (C), 40.8 (CH_2), 53.9 (CH_3), 81.8 (C), 118.3 (CH), 119.2 (CH), 120.5 (2CH), 127.5 (2C), 128.0 (C), 128.9 (2CH), 132.4 (C), 137.3 (C), 138.3 (C), 152.8 (C), 167.4 (C), 170.5 (C); IR (film) 670, 868, 1050, 1157, 1226, 1542, 1665, 1750, 3311 cm^{-1}; HRMS (ESI) Calcd for $C_{22}H_{23}N_3O_5Cl_2$ 480.3, found 480.1056 $(M + H)^+$, 502.0907 $(M + Na)^+$.

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