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Chiral recognition with a benzofuran receptor that mimics an oxyanion hole†

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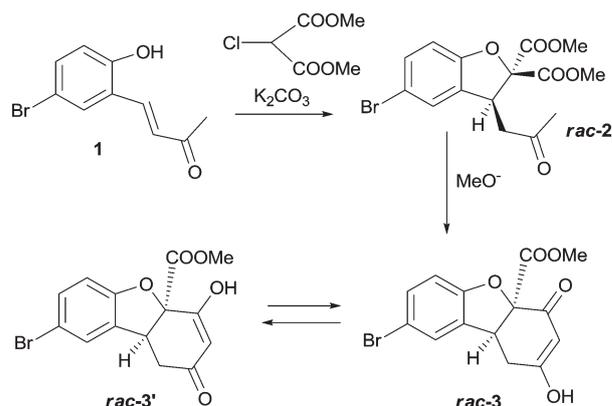
A new chiral benzofuran receptor has been synthesized and its properties in the association of amino acid derivatives have been studied. X-ray structures were obtained and these corroborate the presence of an oxyanion-hole motif in these structures.

Introduction

For decades, chemists have tried to imitate the action mode of natural enzymes to create better catalysts through the development of simpler molecules that resemble the active center of enzymes.¹ The oxyanion hole is a common feature in many enzymes which catalyze reactions in which a carbonyl group is associated: at the active site, two NHs from the protein backbone establish strong linear H-bonds with the carbonyl oxygen.² In the literature, several groups have used the oxyanion-hole strategy to create more efficient catalysts for different reactions.³ In our group we have experience in the preparation of molecular receptors that mimic oxyanion holes: chromenone, xanthene and acridine derivatives have shown good results in amino acid derivatives recognition.⁴ The previous scaffolds are, however, planar heterocycles, which do not help in chiral recognition.

Results and discussion

Based on the easy and attractive preparation of benzofuran 2 from methyl chloromalonate and (*E*)-4-(5-bromo-2-hydroxy-



Scheme 1 Cyclization of racemic compound 2.

phenyl) but-3-en-2-one 1,⁵ we attempted to transform compound 2 into a chiral receptor for carbonyl groups that would mimic an oxyanion hole. Although the final product expected is the racemic one, using the supramolecular properties of the receptor we should be able to resolve its racemic mixture.

Treatment of compound 2 with sodium methoxide yielded the expected intramolecular Claisen reaction (Scheme 1). Compound *rac*-3 shows a complex NMR spectrum because it is a tautomeric mixture of two possible enols and the diketone. Nevertheless, despite having an attractive asymmetric skeleton it still lacks the oxyanion-hole structure.

Modelling studies revealed that direct amination of the aromatic ring provides a cleft that is too wide for an oxyanion-hole mimic (Fig. 1, left). The distance between the amine group and a hypothetical amide on the carboxyl group lies at around 5.1 Å, which is by far larger than the 4.6 Å of the natural oxyanion holes.⁶

To reduce this distance, functionalization with a sulfonamide seemed to be a reasonable strategy, because in this new molecule the cleft was reduced to 4.7 Å (Fig. 1, right).

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†Electronic supplementary information (ESI) available: Experimental procedures, ¹H and ¹³C NMR, IR and HRMS spectra of compounds 1–8 and guests of Tables 2–4, modeling studies of Fig. 1 and 7 and X-ray diffraction data of compounds 6 and 7, determination of the absolute configuration of (+)-7 and (+)-8 by simulation of ECD spectra. CCDC 1010318–1010319. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ob01954g

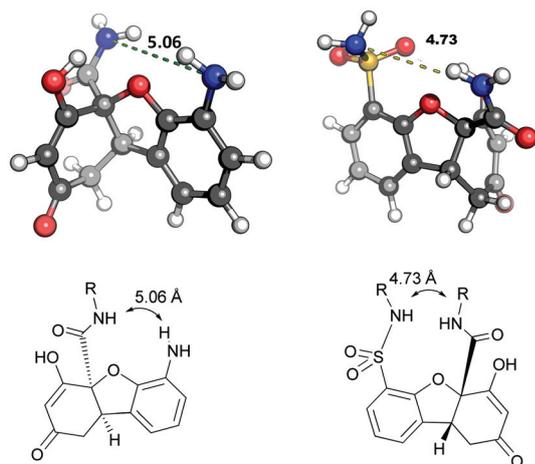
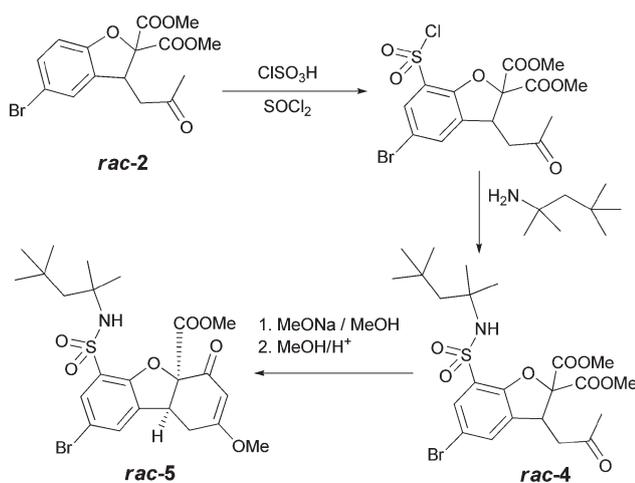


Fig. 1 Distance between the H-bond donors in different possible oxyanion-hole mimics.

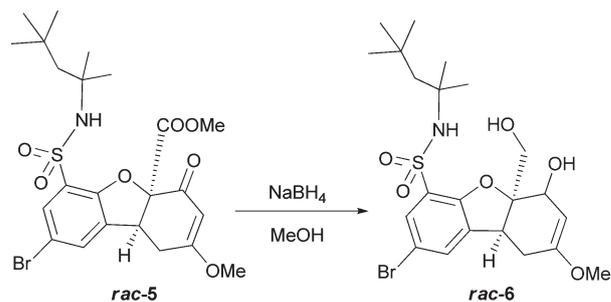


Scheme 2 Preparation of racemic compound 5.

Since modelling studies suggested the sulfonamide as a suitable group for an oxyanion-hole mimic, the synthesis of a first receptor was undertaken. The preparation of this compound is shown in Scheme 2 and, since the diketone shows up as a tautomer mixture, the enoether was prepared by treatment with methanol under acidic conditions. Fortunately, the enoether is formed as a single isomer.

Since compound *rac-5* lacks the necessary second H-bond to mimic an oxyanion hole, reduction with sodium borohydride was carried out. Surprisingly, both the carbonyl and the ester groups underwent the reaction at a similar rate, and hence the diol *rac-6* was obtained (Scheme 3).

An X-ray diffraction study of compound *rac-6* was possible[‡]. The crystals of this receptor show a dimeric structure in which the oxyanion-hole structure is formed between the sulfon-



Scheme 3 Racemic receptor 6 obtained from the sodium borohydride reduction.

amide NH and the secondary hydroxyl group, with a cleft width of 4.7 Å. The primary hydroxyl group of another molecule plays the role of the guest, forming two linear H-bonds in the oxyanion-hole of 2.7 and 2.8 Å (Fig. 2).

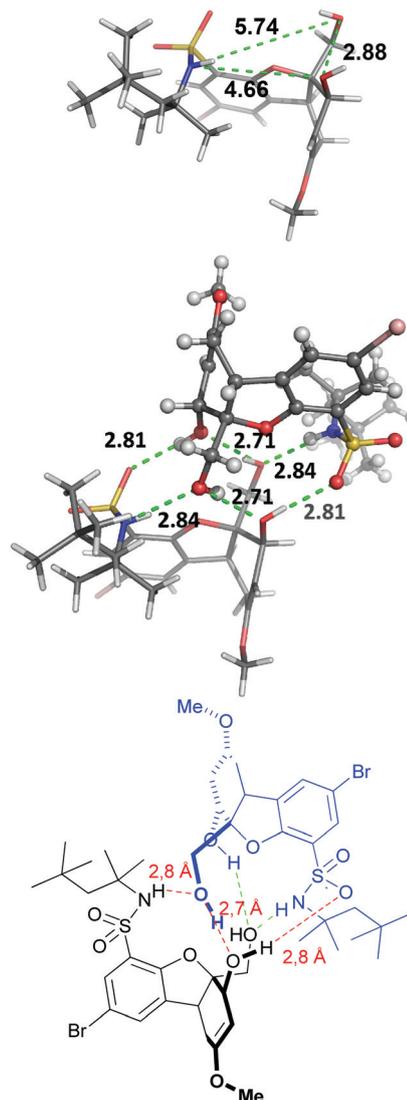
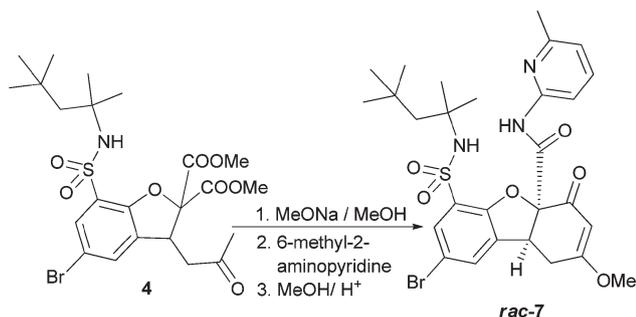


Fig. 2 Solid structure of racemic receptor 6.

[‡] Crystallographic data deposited at the Cambridge Crystallographic Data Centre with the following deposition numbers: CCDC 1010318–1010319.



Scheme 4 Preparation of racemic receptor 7.

To improve the association of carboxylic acid groups, a 6-methyl-2-aminopyridine unit was included in the basic structure of receptor *rac-6*, yielding receptor *rac-7*. 2-Aminopyridine is a common motif in receptors for carboxylic acids.⁷ The preparation of this new receptor is straightforward, since the aminopyridine reacts with the ester group under the basic conditions used for cyclization, as shown in Scheme 4.

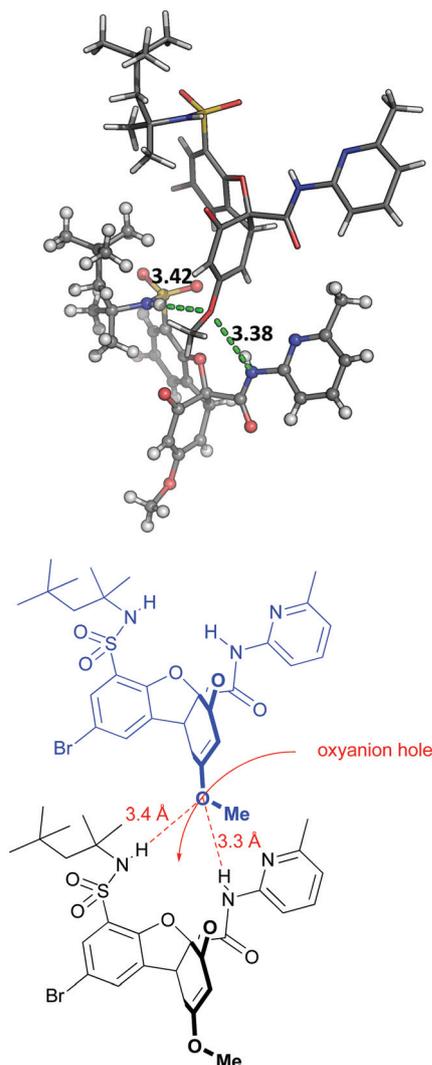


Fig. 3 Solid structure of racemic receptor 7.

It is also possible to determine the detailed structure of the solid receptor 7‡. X-ray analysis again revealed the presence of the oxyanion hole (Fig. 3). In this case, the methoxy group is the oxyanion-hole guest, showing long H-bonds with the receptor donors, probably because this oxygen is a poor H-bond acceptor.

Receptor *rac-7* was tested as an acid receptor with simple carboxylic acids (Fig. 4). Association constants were measured in deuteriochloroform at 20 °C using standard procedures,⁸ and the results in Table 1 clearly show an increase in the association constant with the guest acidity.

The cooperation of both receptor NHs in the carbonyl group's association is clear from the NMR spectra since both underwent strong deshieldings, moving from 5.72 ppm to 6.49 ppm (for the sulfonamide NH; the carboxamide NH is difficult to follow because it becomes too broad).

Since the association constants were below our expectations, we tested the effect of the possible intramolecular H-bonding between the carboxamide NH and the furan oxygen. The racemic model structure shown in Fig. 5 was allowed to compete for trichloroacetic acid with a simple aminopyridine benzamide. The benzamide formed a complex fifty-fold stronger than the furan derivative, showing that the intramolecular H-bonding had a weakening effect on the carboxylic group association.

Amino acid derivatives are expected to show larger association constants, since they may form a fourth H-bond between the amino acid NH and one of the sulfonyl oxygens, as shown in Fig. 6.

According to Ogston's three-point model to explain enantioselectivity of some reactions catalyzed by enzymes,⁹ for a chiral receptor to be able to discriminate between two enantiomeric species, at least three points of the receptor must interact with

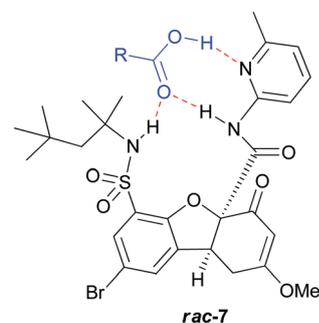


Fig. 4 Proposed geometry of racemic receptor 7 associated with a carboxylic acid.

Table 1 Association constants between receptor *rac-7* and carboxylic acids with increasing acidity

| Entry | Guest | pK _a (H ₂ O) | K _{ass} (M ⁻¹) |
|-------|-----------------------|------------------------------------|-------------------------------------|
| 1 | CH ₃ COOH | 4.76 | 360 |
| 2 | CCl ₃ COOH | 0.65 | 500 |
| 3 | CF ₃ COOH | -0.25 | 1700 |

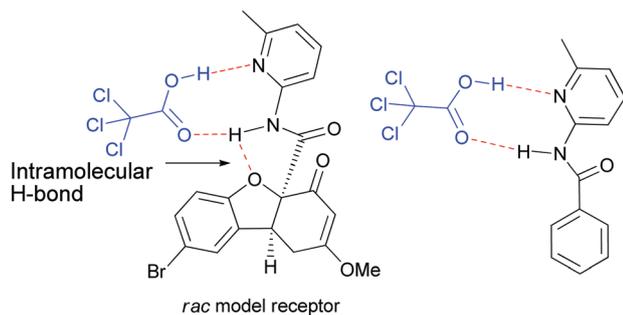


Fig. 5 Associates studied to assess the effect of the intramolecular H-bond in the association stability. The furan associate is 50-fold weaker than the benzoylaminopyridine.

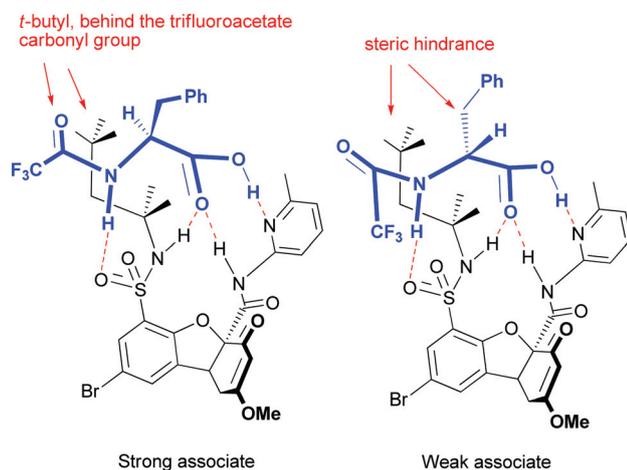


Fig. 6 Strong and weak complexes of L and D trifluoroacetylphenylalanine and the receptor (-)-7.

three complementary points of the compound which has to be accommodated. The complex formed between receptor 7 and amino acid derivatives should fulfil this model: the first interaction would be of acid–base nature between carboxylic acid and aminopyridine with the oxyanion-hole collaboration; the second interaction would be the additional H-bond between amino acid NH and one of the sulfuryl oxygens; and the third interaction would be determined by a bulky group in the amino acid α -position, which would show preference for one enantiomer but not for the other.

The effect of the additional H-bond in the amino acid derivative was tested with a competitive titration between phenylacetic acid and trifluoroacetylphenylglycine. This afforded a competitive constant of 14 in favour of the guest with the additional NH, which is consistent with the four H-model proposed for the association of the amino acid.

The amino acid association model also predicts some degree of chiral discrimination, since the enantiomers of amino acids with side chains should point these groups in different spatial directions. In particular, one of the enantiomers should place the side chain close to the *t*-octyl group, leading to steric hindrance.

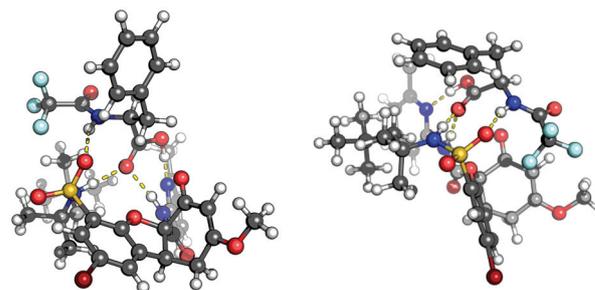


Fig. 7 Complexes obtained by modelling study between the receptor (-)-7 and trifluoroacetyl-L-phenylalanine (left) and trifluoroacetyl-D-phenylalanine (right).

The chiral recognition of receptor *rac*-7 was tested in a competitive titration with trifluoroacetyl-L-phenylalanine. Adding the amino acid derivative to the receptor racemic mixture led to a clear splitting of most of the receptor signals, revealing the formation of two diastereomeric complexes.

The large singlets of the *t*-butyl groups of the enantiomeric receptors offer an easy way to follow the competitive titration. From the movement of these signals it is possible to deduce a ratio of 2.2 between the stability constants of the receptor enantiomers.

The relatively strong shielding effect observed for the *t*-butyl group in the strong complex can be explained with the geometry shown in Fig. 6, since this group lies in the anisotropic shielding cone of the trifluoroacetate carbonyl group. The weak complex lacks this shielding effect, which explains the large split observed in the *t*-butyl group of both the strong and the weak complexes.

A modelling study (DFT calculations were performed using the Gaussian09¹⁰ program and the functional M06-2X¹¹ was combined with the 6-31G**¹² basis set in the gas phase) shown in Fig. 7 confirmed the proposed geometry, therefore, the (4*aR*,9*bS*) receptor is the enantiomer which forms the strong complex with the natural L amino acid.

The geometry of these associates was confirmed with a NOE effect between the amino acid alpha proton and the receptor *t*-butyl group which only lie close to each other in the strong complex (ESI). Since in the weak complex the amino acid side chain faces the large receptor *t*-butyl group, steric hindrance is a good explanation for the chiral discrimination in these associates.

To validate the proposed model, the circular dichroism spectrum of the receptor was studied. TD-DFT calculations (B98 functional) nicely reproduce the positive sign of the band at 285 nm ($\epsilon = 9.3$) and the negative value of the band at 315 nm ($\epsilon = 6.5$) (see ESI[†]), supporting again the proposed configuration.

To further confirm the absolute configuration, the vinyl ether (+)-7 was hydrolysed in aqueous THF, yielding compound (+)-8 (Fig. 8).

The NMR spectrum of compound (+)-8 shows that it is in its enol form. However to assign the absolute stereochemistry it is necessary to know which carbon is supporting the keto

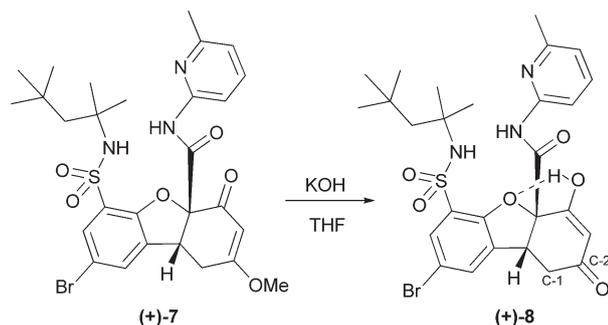


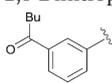
Fig. 8 Hydrolysis of compound (+)-7.

group. A long range C–H correlation between the C-1 methylene protons and the carbonyl carbon places unambiguously the ketone at the C-2 carbon,¹³ while the enol is probably closing an intramolecular H-bond with the furan oxygen (ESI). The circular dichroism spectrum shows two bands at 245 nm ($\epsilon = 6.5$) and 290 nm ($\epsilon = 11$), which were reproduced by TD-DFT calculations (B98 functional).

Other amino acid derivatives showed similar results to trifluoroacetyl-L-phenylalanine. From the corresponding competitive titrations it was possible to measure the values shown in Tables 2 and 3.

Since there was a clear discrimination between an optically pure amino acid derivative and the receptor enantiomers we attempted to resolve the racemic mixture of the receptor based on this discrimination. Trifluoroacetyl-L-phenylalanine was selected as the guest. Impregnation of the TLC plates with a 1.5% solution of the optically active guest in chloroform yielded a stationary phase that was useful for the separation of the receptor enantiomers. Elution of the receptor mixture with methylene chloride several times afforded two different spots

Table 3 Relative association constants between amino acid derivatives and racemic receptor 7

| Entry | Guest | R ₁ | R ₂ | K _{rel} |
|-------|-------|--|----------------------|------------------|
| 1 | 26 | CF ₃ | Ph | 1.3 |
| 2 | 27 | CF ₃ | Bn | 2.1 |
| 3 | 28 | 2,5-Dinitrophenyl | Ethylhexylthiomethyl | 1.7 |
| 4 | 29 |  | Me | 1.5 |

with R_f 0.5 and R_f 0.4 for the receptor enantiomers. Scale-up of this experiment by impregnating 16 g SiO₂ preparative plates allowed the separation of 20 mg of mixture on each plate. Workup of the ethylacetate solution with sodium carbonate allowed the release of the free receptor 7.

The resolution of the racemic mixture allowed the measurement of the absolute association constant between each of the enantiomers of receptor 7 and trifluoroacetyl-L-phenylalanine. A standard titration using a constant receptor concentration in deuteriochloroform provided a large constant with a value of 6700 M⁻¹ for the strong complex. The stability constant for the weak associate was calculated to be 3350 M⁻¹.

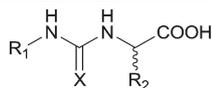
The free receptor can be used in enantioselective extractions of racemic amino acid derivatives. To check the enantioselectivity of these extractions, the racemic guest in a chloroform solution (0.5 mL, 1 × 10⁻² M) was treated with 1.1 eq. of (+)-7. The ¹H NMR spectrum showed the splitting of the guest's signals, due to formation of the diastomeric guest–host complexes. Treating this sample with an aqueous solution

Table 2 Relative association constants between amino acid derivatives and racemic receptor 7

| Entry | Guest | R ₁ | X ₁ | X ₂ | R ₂ | K _{rel} |
|-------|-------|---------------------------------|----------------|----------------|------------------|------------------|
| 1 | 9 | Bn | O | O | Me | 1.3 |
| 2 | 10 | <i>t</i> -Bu | O | O | <i>i</i> -Bu | 2.1 |
| 3 | 11 | Bn | O | O | Bn | 1.7 |
| 4 | 12 | <i>n</i> -Bu | NH | O | <i>i</i> -Pr | 1.5 |
| 5 | 13 | <i>n</i> -Bu | NH | O | Ph | 1.0 |
| 6 | 14 | <i>n</i> -Bu | NH | O | Me | 4.2 |
| 7 | 15 | Bis-3,5-(trifluoromethyl)phenyl | NH | O | Me | 1.6 |
| 8 | 16 | Ph | NH | O | <i>i</i> -Bu | 1.3 |
| 9 | 17 | Cyclohexyl | NH | S | Me | 6.6 |
| 10 | 18 | <i>n</i> -Decyl | NH | S | Me | 6.0 |
| 11 | 19 | Bis-3,5-(trifluoromethyl)phenyl | NH | S | Me | 3.5 |
| 12 | 20 | <i>n</i> -Decyl | NH | S | <i>i</i> -Bu | 4.2 |
| 13 | 21 | Bis-2,6-(isopropyl)phenyl | NH | S | Me | 2.5 |
| 14 | 22 | Cyclohexyl | NH | S | <i>i</i> -Pr | 2.3 |
| 15 | 23 | Cyclohexyl | NH | S | Methylthiomethyl | 2.5 |
| 16 | 24 | <i>t</i> -Octyl | NH | S | Me | 2.0 |
| 17 | 25 | Bis-3,5-(trifluoromethyl)phenyl | NH | S | Bn | 1.5 |

Table 4 Enantiomeric extractions carried out with receptor (+)-7

| Entry | Guest | X | R ₁ | R ₂ | Enantiomeric ratio |
|-------|----------------|---|-------------------|----------------|--------------------|
| 1 | <i>rac</i> -17 | S | Cyclohexyl | Me | 2.5 : 1 |
| 2 | <i>rac</i> -30 | O | 3,5-Dinitrophenyl | <i>i</i> -Bu | 1 : 1 |
| 3 | <i>rac</i> -31 | O | Phe | Phe | 1 : 1 |
| 4 | <i>rac</i> -32 | O | <i>n</i> -Bu | Bn | 1.3 : 1 |
| 5 | <i>rac</i> -33 | O | <i>t</i> -Bu | Bn | 2 : 1 |



of the racemic guest lithium salt (10 eq., 0.5 mL) resulted in a large increase in the NMR signals of the strong associate, while the weak one reduces its intensity. Integration of the signals allowed the calculation of the relative association constant. The results are shown in Table 4.

Conclusions

To summarize, a new benzofuran-based receptor has been synthesized. It was functionalized to create an oxyanion-hole motif in its structure with the aim of associating amino acid derivatives in a similar way to what enzymes do in nature. The resolution of the receptor racemic mixture was carried out making use of its supramolecular properties by preparative silica gel chromatography. The enantiomerically pure receptor shows a moderate enantiomeric ratio in chiral extractions of amino acid ureas and thioureas.

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 $^{\circ}\text{C}$. NMR spectra were recorded on 200 MHz and 400 MHz spectrometers. ^1H NMR chemical shifts are reported in ppm with tetramethylsilane (TMS) as an internal standard. Data for ^1H 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. Flash chromatography was performed on 70–200 mesh silica gel.

(*E*)-4-(5-Bromo-2-hydroxyphenyl) but-3-en-2-one (1). An aqueous solution of NaOH 1.2 M was added through an

addition funnel to a solution of 5-bromo-2-hydroxybenzaldehyde (290 g, 1.44 mol) in 1.4 L of acetone. After the addition, stirring was maintained for 1 hour. Then, the reaction mixture was poured over ice and concentrated HCl, observing the appearance of a solid. The solid obtained was filtered and allowed to dry at room temperature, yielding 350 g of the desired product **1** with a yield of 84%. Mp 148–149 $^{\circ}\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm) 2.29 (3H, s), 6.88 (1H, d, $J = 8.7$ Hz), 6.90 (1H, d, $J = 16.4$ Hz), 7.37 (1H, dd, $J = 2.5, 8.7$ Hz), 7.68 (1H, d, $J = 16.4$ Hz), 7.77 (1H, d, $J = 2.5$ Hz); ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) δ (ppm) 27.6 (CH₃), 110.7 (C), 118.3 (CH), 123.3 (C), 127.8 (CH), 130.6 (CH), 133.8 (CH), 136.7 (CH), 156.1 (C), 198.0 (C); IR (film) ν 3054, 1628, 1593, 1259, 748 cm^{-1} ; HRMS Calcd for C₁₀H₁₀O₂Br 240.9859, found 240.9865.

Dimethyl-5-Bromo-3-(2-oxopropyl)-benzofuran-2,2(3*H*)-dicarboxylate (2). Chalcone **1** (160 g, 0.66 mol), dimethyl chloromalonate (200 mL, 1.16 mol), K₂CO₃ (170 g, 1.23 mol) and DMF (590 mL) were added into a round-bottomed flask. The reaction mixture was kept under stirring for 2 hours at room temperature, monitoring the reaction progress by ^1H NMR. After the reaction had been completed, the mixture was poured onto a mixture of water, ice, hexane, ether and concentrated HCl and stirred; a precipitate was formed. The obtained solid was vacuum-filtered, washed with water and dried. The product was purified by crystallization in MeOH at 0 $^{\circ}\text{C}$, yielding 250 g of the pure product **2** with 66% yield. Mp 90–93 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl₃) δ (ppm) 2.16 (3H, s), 2.71 (1H, dd, $J = 8.9, 18.0$ Hz), 2.87 (1H, dd, $J = 4.9, 18.0$ Hz), 3.78 (3H, s), 3.80 (3H, s), 4.68 (1H, dd, $J = 4.9, 8.9$ Hz), 6.76 (1H, d, $J = 8.5$ Hz), 7.17 (1H, d, $J = 2.0$ Hz), 7.23 (1H, dd, $J = 2.0, 8.5$ Hz); ^{13}C NMR (100 MHz, CDCl₃) δ (ppm) 30.1 (CH₃), 43.0 (CH), 44.9 (CH₂), 53.2 (CH₃), 53.7 (CH₃), 91.9 (C), 111.6 (CH), 114.1 (C), 127.7 (CH), 130.5 (C), 131.8 (CH), 156.3 (C), 166.9 (C), 167.4 (C), 204.7 (C); IR (film) ν 3049, 1747, 1474, 1274, 1055, 743 cm^{-1} ; HRMS Calcd for C₁₅H₁₆O₆Br 371.0125, found 371.0131.

Dimethyl-5-Bromo-7-(chlorosulfonyl)-3-(2-oxopropyl)-benzofuran-2,2(3*H*)-dicarboxylate. Into a two-necked flask equipped with a magnetic stirrer, a low-temperature thermometer and an addition funnel under an argon atmosphere, thionyl chloride (60 mL, 0.83 mol) was added and cooled in an ice-salt bath. Once the temperature had fallen below 0 $^{\circ}\text{C}$, the intermediate **2** (30.3 g, 0.082 mol) plus chlorosulfonic acid (60 mL, 0.90 mol) were added through the addition funnel, allowing the contents to drip through slowly ensuring that the temperature did not exceed 5 $^{\circ}\text{C}$ at any time. Once the addition was complete, the mixture was maintained at a temperature of 5 $^{\circ}\text{C}$ for 62 hours, monitoring the reaction progress by ^1H NMR. Once the reaction had finished, it was diluted with CH₂Cl₂ (200 mL) and slowly poured onto a mixture of CH₂Cl₂ and ice with stirring. Then, the phases were separated, the organic phase was dried over anhydrous Na₂SO₄, and the solvent was removed by evaporation under vacuum to yield 37.0 g of the title product with 96% yield. Mp 124–126 $^{\circ}\text{C}$; ^1H NMR (400 MHz, CDCl₃) δ (ppm) 2.23 (3H, s), 2.78 (1H, dd, $J = 9.4, 18.3$ Hz), 3.04 (1H, dd, $J = 4.1, 18.3$ Hz), 3.84 (3H, s), 3.88 (3H,

s), 4.75 (1H, dd, $J = 4.1, 9.4$ Hz), 7.54 (1H, d, $J = 1.9$ Hz), 7.85 (1H, d, $J = 1.9$ Hz); ^{13}C NMR (50 MHz, CDCl_3) δ (ppm) 30.1 (CH_3), 42.7 (CH), 44.2 (CH_2), 53.7 (CH_3), 54.1 (CH_3), 93.2 (C), 113.9 (C), 127.2 (C), 129.5 (CH), 134.5 (C), 135.2 (CH), 153.8 (C), 165.5 (C), 166.2 (C), 204.6 (C); IR (nujol) ν 2916, 2949, 2852, 1768, 1748, 1723, 1599, 1456, 1372, 1301, 1242, 1184, 1165, 1061 cm^{-1} ; HRMS Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_8\text{S}\text{ClBr}$ 485.9620, found 485.9629.

Dimethyl-5-bromo-3-(2-oxopropyl)-7-(*N*-(2,4,4-trimethylpentan-2-yl)sulfamoyl)benzofuran-2,2(3*H*)dicarboxylate (4). A solution of the previous chlorosulfonyl compound (11.8 g, 1 mmol) in 81 mL of EtOAc was added to a solution of *t*-octylamine (6.13 g, 47.4 mmol) and triethylamine (5.5 mL, 39.7 mmol) in 27 mL of EtOAc and the mixture was stirred at room temperature for 5 hours. When the reaction was complete it was added to 2 M HCl (200 mL) with ice. The organic phase was separated, dried and evaporated. The obtained solid was purified by crystallization with EtOAc, yielding 5.3 g of the desired compound (38% yield). Mp 138–140 °C; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 1.01 (9H, s), 1.23 (3H, s), 1.25 (3H, s), 1.58 (1H, d, $J = 14.9$ Hz), 1.63 (1H, d, $J = 14.9$ Hz), 2.19 (3H, s), 2.75 (1H, dd, $J = 8.7, 18.2$ Hz), 2.96 (1H, dd, $J = 4.4, 18.2$ Hz), 3.80 (3H, s), 3.83 (3H, s), 4.69 (1H, dd, $J = 4.4, 8.7$ Hz), 4.94 (NH, s), 7.33 (1H, s), 7.76 (1H, s); ^{13}C NMR (100 MHz, CDCl_3) δ (ppm) 29.1 (CH_3), 29.2 (CH_3), 30.0 (CH_3), 31.6 (CH_3), 32.9 (C), 42.8 (CH), 44.5 (CH_2), 53.4 (CH_3), 53.9 (CH_3), 54.7 (CH_2), 58.9 (C), 92.3 (C), 113.9 (C), 128.1 (C), 129.6 (CH), 131.4 (CH), 132.3 (C), 152.4 (C), 165.9 (C), 166.6 (C), 204.5 (C); IR (film) ν 3358, 2962, 2903, 1755, 1710, 1593, 1463, 1327, 1236, 1158, 1100, 1061, 1035, 743 cm^{-1} ; HRMS Calcd for $\text{C}_{23}\text{H}_{36}\text{BrN}_2\text{O}_8\text{S}$ 579.1373, found 579.1365.

Methyl 8-bromo-2-methoxy-4-oxo-6-(*N*-(2,4,4-trimethylpentan-2-yl)sulfamoyl)-1,4,4a,9b-tetrahydrobenzo[*b,d*]furan-4a-carboxylate (*rac*-5). Under an argon atmosphere, Na (1.0 g, 43.5 mmol) was added to 10 mL of MeOH (50 mL of MeOH were previously dried with 3.0 mL of methyl orthoformate and one drop of methanesulfonic acid). When the sodium was completely dissolved, the mixture was cooled in an ice bath and then compound 4 (3.8 g, 6.8 mmol) was added. The ice bath was removed and within minutes a solid began to crystallize. After 30 minutes, the reaction mixture was added to a solution of methyl orthoformate (4.9 mL, 44.8 mmol) and methanesulfonic acid (4.9 mL, 75.6 mmol) in dry MeOH (28 mL) at -10 °C. Then, the mixture was allowed to reach room temperature and Na_2CO_3 (8.4 g, 79.7 mmol) in water (70 mL) was added. Following this, MeOH were evaporated and the aqueous solution was extracted with EtOAc, affording 3.1 g of the desired compound (84% yield). This compound was purified by silica gel column chromatography with CH_2Cl_2 -EtOAc as eluents, yielding 1.3 g with a final yield of 34%. Mp 175–177 °C; ^1H NMR (200 MHz, CDCl_3) δ (ppm) 0.99 (9H, s), 1.17 (3H, s), 1.19 (3H, s), 1.52 (1H, d, $J = 14.8$ Hz), 1.64 (1H, d, $J = 14.8$ Hz), 2.80 (1H, dd, $J = 3.2, 18.2$ Hz), 3.19 (1H, dd, $J = 7.4, 18.2$ Hz), 3.71 (3H, s), 3.80 (3H, s), 4.19 (1H, dd, $J = 3.2, 7.4$ Hz), 5.27 (1H, s), 5.52 (1H, s), 7.36 (1H, s), 7.73 (1H, s); ^{13}C NMR (50 MHz, CDCl_3) δ (ppm) 28.9 (CH_2), 29.1

(CH_3), 29.4 (CH_3), 31.6 ($\text{CH}_3 \times 3$), 31.6 (C), 42.1 (CH), 53.5 (CH_3), 54.4 (CH_2), 56.5 (CH_3), 59.1 (C), 89.6 (C), 102.3 (CH), 113.9 (C), 128.6 (C), 129.8 (CH), 129.9 (CH), 131.8 (C), 152.8 (C), 167.5 (C), 176.0 (C), 187.4 (C); IR (nujol) ν 3332, 3079, 2949, 2929, 2852, 1768, 1651, 1606, 1456, 1411, 1353, 1307, 1255, 1210, 1165, 1139, 1093, 1041, 983 cm^{-1} ; HRMS Calcd for $\text{C}_{23}\text{H}_{34}\text{BrN}_2\text{O}_7\text{S}$ 561.1265, found 561.1264.

2-Bromo-6-hydroxy-5a-(hydroxymethyl)-8-methoxy-*N*-(2,4,4-trimethylpentan-2-yl)-5a,6,9,9a-tetrahydrobenzo[*b,d*]furan-4-sulfonamide (*rac*-6). Compound 5 (250 mg, 0.46 mmol) was dissolved in MeOH (6 mL) and NaBH_4 (34 mg, 0.90 mmol) was added. The reaction was monitored by TLC, using CH_2Cl_2 -EtOAc as eluents. When the reaction was complete, the mixture was diluted with EtOAc and then 18 mL of 0.6 M aqueous NH_4Cl was added. Then, the organic phase was separated, dried and evaporated to give 210 mg of compound 6, which was purified by crystallization using CH_2Cl_2 , obtaining 68 mg (29% yield). Mp 128–130 °C; ^1H NMR (400 MHz, CD_3OD) δ (ppm) 1.05 (9H, s), 1.14 (3H, s), 1.18 (3H, s), 1.50 (1H, d, $J = 14.7$ Hz), 1.70 (1H, d, $J = 14.7$ Hz), 2.36 (1H, dd, $J = 2.5, 15.5$ Hz), 2.53 (1H, dd, $J = 6.8, 15.5$ Hz), 3.39 (3H, s), 3.78 (1H, dd, $J = 2.5, 6.8$ Hz), 3.85 (2H, s), 4.46 (1H, s), 4.58 (1H, s), 7.51 (1H, d, $J = 2.0$ Hz), 7.58 (1H, d, $J = 2.0$ Hz); ^{13}C NMR (100 MHz, CD_3OD) δ (ppm) 29.4 (CH_3), 30.8 (CH_3), 32.2 ($\text{CH}_3 \times 3$), 32.6 (C), 33.3 (CH_2), 42.7 (CH), 55.1 (CH_3), 55.6 (CH_2), 58.8 (C), 64.9 (CH_2), 68.5 (CH), 96.7 (C), 98.7 (CH), 112.4 (C), 127.9 (C), 130.1 (CH), 132.4 (CH), 138.3 (C), 156.6 (C), 156.9 (C); IR (film) ν 3455, 3221, 3105, 2923, 2832, 2728, 2670, 1677, 1586, 1463, 1379, 1314, 1262, 1236, 1216, 1139, 1041, 892, 814, 736; HRMS Calcd for $\text{C}_{22}\text{H}_{36}\text{BrN}_2\text{O}_6\text{S}$ 535.1472, found 535.1471.

8-Bromo-2-methoxy-*N*-(6-methylpyridin-2-yl)-4-oxo-6-(*N*-(2,4,4-trimethylpentan-2-yl)sulfamoyl)-1,4,4a,9b-tetrahydrobenzo[*b,d*]furan-4a-carboxamide (*rac*-7). A solution of Na (6.0 g, 0.26 mol) was prepared in 75 mL of MeOH (previously dried using 3.0 mL of methyl orthoformate and two drops of methanesulfonic acid). When the sodium was completely dissolved it was cooled in an ice-salt bath and compound 4 (25.0 g, 0.044 mol) was added. The temperature was raised to 10 °C. Initially compound 4 dissolved slowly in the reaction medium, but then the appearance of a precipitate was observed. To follow the progress of the reaction, an aliquot was added over water acidified with MeSO_3H , precipitating a white solid, whose ^1H NMR analysis indicated that its structure corresponded to the cyclization product. At this moment, 2-amino-6-methylpyridine (15.8 g, 0.15 mol) and 20 mL of dry THF were added to the reaction medium. The solution was refluxed for two hours, until all the solid had dissolved. Then, the reaction mixture was cooled and added to methanesulfonic acid (50 mL) in water and ice, and the obtained solid was filtered. The mother liquors were extracted with EtOAc; the layers were separated, and after evaporation of the organic solvent the obtained product could be coupled with the above solid to afford 25.0 g of the enol (94% yield).

Following this, the enol prepared in the previous step was added (2.38 g, 3.92 mmol) to a solution of methyl orthoformate (3.0 mL, 27 mmol) and acetyl chloride (350 μL ,

4.92 mmol) in 18 mL of MeOH and cooled in an ice bath and the solution was stirred. The reaction was monitored by TLC (DCM–EtOAc 1:1). The ice bath was removed and within minutes a precipitate corresponding to the hydrochloride of compound 7 appeared. The solid thus obtained was filtered, obtaining 1.0 g of compound 7 as the hydrochloride. Solid Na₂CO₃ was added to the filtrate, and the carbonate was filtered off and washed with more EtOAc. The solution was left to stand for 12 h and a precipitate, which corresponded to the neutral compound 7 (700 mg), appeared. Receptor 7 hydrochloride was suspended in CHCl₃ and washed with aqueous saturated Na₂CO₃ yielding 0.5 g of compound 7 (total yield 49%). Mp >230 °C; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.03 (9H, s), 1.23 (6H, s), 1.48 (1H, d, *J* = 14.9 Hz), 1.74 (1H, d, *J* = 14.9 Hz), 2.46 (3H, s), 2.89 (1H, d, *J* = 18.1 Hz), 3.40 (1H, dd, *J* = 7.2, 18.1 Hz), 3.76 (3H, s), 4.39 (1H, d, *J* = 7.2 Hz), 5.45 (NH, s), 5.60 (1H, s), 6.93 (1H, d, *J* = 7.6 Hz), 7.42 (1H, s), 7.57 (1H, t, *J* = 7.9 Hz), 7.84 (1H, s), 7.89 (1H, d, *J* = 8.2 Hz), 9.23 (NH, s); ¹³C NMR (100 MHz, CDCl₃) δ (ppm) 23.9 (CH₃), 29.0 (CH₂), 29.2 (CH₃), 29.5 (CH₃), 31.6 (CH₃ × 3), 31.6 (C), 41.9 (CH), 54.5 (CH₂), 56.4 (CH₃), 59.1 (C), 90.2 (C), 102.6 (CH), 111.0 (CH), 114.4 (C), 120.2 (CH), 129.0 (C), 129.7 (CH), 130.3 (CH), 132.2 (C), 138.4 (CH), 149.2 (C), 152.2 (C), 157.4 (C), 165.6 (C), 176.2 (C), 188.7 (C); IR (nujol) ν 3377, 3338, 2929, 2955, 2852, 1697, 1664, 1612, 1463, 1379, 1346, 1203, 1145, 1048, 976, 918 cm⁻¹; HRMS Calcd for C₂₈H₃₅BrN₃O₆S 620.1424, found 620.1432.

(4aS,9bR)-8-Bromo-4-hydroxy-N-(6-methylpyridin-2-yl)-2-oxo-6-(N-(2,4,4-trimethylpentan-2-yl)sulfamoyl)-1,2,4a,9b-tetrahydrodibenzo[*b,d*]furan-4a-carboxamide ((+)-8). Compound (+)-7 (100 mg, 0.16 mmol) was dissolved in a homogeneous mixture of THF–H₂O (9:1) and *p*TsOH (30.3 mg, 0.18 mmol) was added. After 12 h, the reaction mixture was added over a sodium formate solution and extracted with EtOAc, yielding 60 mg of (+)-8 (62% yield). [α]_D²⁰ = +212.3 (*c* = 0.99, CHCl₃); mp: 228–230 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ (ppm) 0.94 (9H, s), 1.09 (3 H, s), 1.19 (3H, s), 1.42 (1H, d, *J* = 14.6 Hz), 1.63 (1H, d, *J* = 14.6 Hz), 2.41 (3H, s), 3.00 (2H, br s), 4.44 (1H, t, *J* = 5.1 Hz), 5.47 (1H, s), 7.06 (1H, d, *J* = 7.3 Hz), 7.63 (1H, d, *J* = 2.6 Hz), 7.72 (1H, dd, *J* = 7.3, 8.0 Hz), 7.80 (1H, d, *J* = 8.0 Hz), 7.83 (1H, s), 9.99 (NH, s); ¹³C NMR (100 MHz, DMSO-*d*₆) δ (ppm) 23.5 (CH₃), 28.7 (CH₃), 29.1 (CH₃), 31.0 (CH₂), 31.2 (C), 31.4 (CH₃ × 3), 41.8 (CH), 53.6 (CH₂), 57.5 (C), 109.1 (C), 111.6 (CH), 112.9 (C), 120.0 (CH), 121.6 (C), 128.7 (CH), 129.1 (C), 130.3 (CH), 134.5 (CH), 138.6 (CH), 149.4 (C), 151.8 (C), 156.9 (C), 166.9 (C), 175.7 (C), 196.9 (C); IR (nujol) ν 3390, 3306, 2916, 2839, 1710, 1606, 1521, 1456, 1366, 1249, 1203, 1152 cm⁻¹; HRMS Calcd for C₂₇H₃₃BrN₃O₆S 606.1268, found 606.1284.

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