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Malonic Acid Receptors With Decarboxylative Activity

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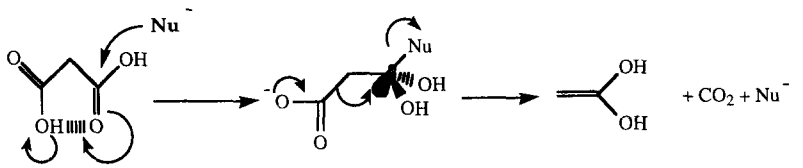
Abstract: The geometry and electronic properties of several malonic acids receptors are studied with a view to optimizing their decarboxylative activity.

The decarboxylation of suitably substituted amidomalonic acids is an old and well known procedure used to prepare aminoacids.[1] The standard conditions, however, lead only to racemic mixtures. A natural enzyme, L-aspartate decarboxylase, is able to induce the chiral decarboxylation of these diacids,[2] and it should therefore be possible to develop an artificial enzyme with similar activity.

A molecule capable of complexing, then inducing decarboxylation and chiral reprotonation of the enol or the enolate of an amidomalonic acid is probably quite complex. Therefore, as a first step we wished to develop only malonic acids receptors , from which decarboxylative activity is expected. Malonic acid has already been complexed, but no decarboxylative activity of these receptors has been reported.[3]

The thermal decarboxylation of malonic acids takes place only at high temperatures, however weak nucleophiles such as pyridine or quinoline strongly catalyze the reaction[4] through a mechanism in which nucleophilic addition to the malonic acid carbonyl group takes place (Scheme 1).

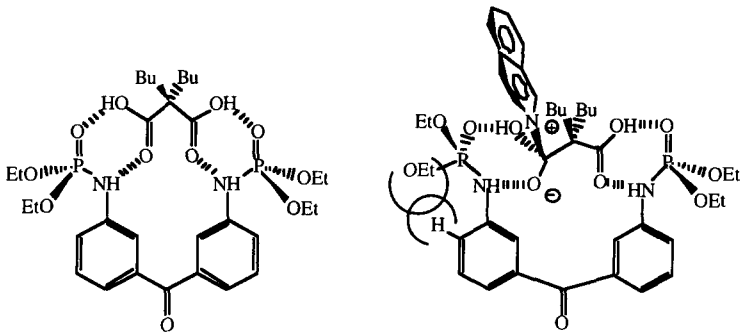


Scheme 1. Proposed Mechanism for Malonic Acid Decarboxylation.

The transition state of this reaction probably resembles the tetrahedral intermediate. In agreement with the Pauling Hypothesis,[5] complexing agents capable of better associating this transition state than the ground state should show catalytic activity. Accordingly complexing agents with a geometry complementary to this transition state have been developed.

An initial receptor **1** based on a benzophenone with two phosphorylamide binding groups showed only weak activity (Table 1).[6] As an active catalyst, this molecule has two serious drawbacks: a) the intramolecular hydrogen bond in malonic acids[7] provides general acid catalysis in the nucleophilic addition step but in the

complex with **1** the intramolecular hydrogen bond is lost and therefore acid catalysis is low; b) steric repulsion between the ortho-aromatic proton and the phosphoryl oxygen atom handicaps the transition state complex (Figure 1).



1 **1**

Figure 1. Proposed Complexes for Receptor **1** with Dibutylmalonic Acid (DBMA) in Ground and Transition State.

To avoid these drawbacks, a new receptor **2** was prepared. The urea binding arm permits complexing of the malonic acid with the intramolecular hydrogen bond, while the formation of the phosphorinane ring sets the right conformation to accommodate the transition state without steric repulsions (Figure 2).

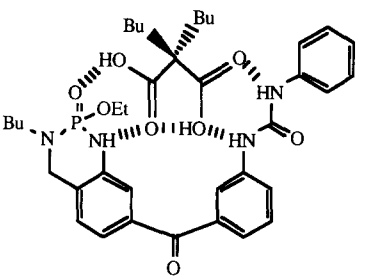


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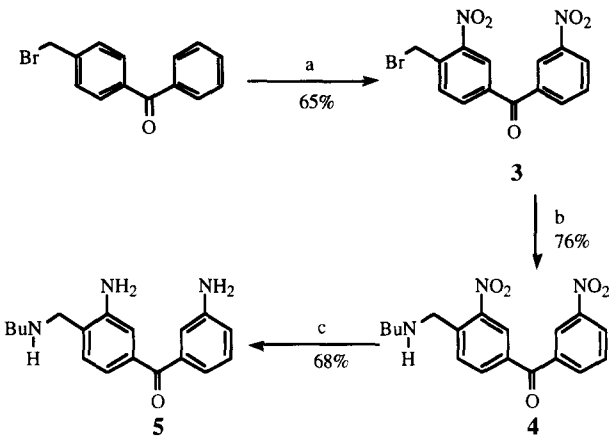
Figure 2. Proposed Complex for Receptor **2** and DBMA.

The starting material for this receptor, triamine **5**, was prepared by a three step route from 4-bromomethyl benzophenone by nitration, displacement of the bromine atom with butylamine, and reduction of the nitro groups without any chromatography (Scheme 2). Receptor **2** was obtained from it with a reasonably high yield using ethyl chlorophosphate and phenyl isocyanate (Scheme 3).

The association constant of receptor **2** with DBMA was higher than that corresponding to receptor **1**, in agreement with a complex in which the intramolecular malonic acid hydrogen bond does not have to be cleaved. Catalytic studies were initially performed by NMR analysis. However, better results were obtained using gas volumetry, as described by Corey.[8] Catalytic activity was also much better than in the preceding case (Table 1). This good result encouraged us to study the influence of phosphorinane ring substituents in receptor activity, as well as the influence of urea residues.



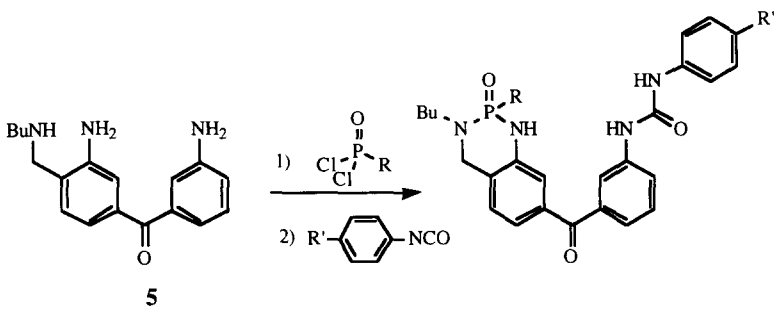
a) HNO_3/H_2SO_4, b) Butylamine/ ethyl acetate, c) $SnCl_2$/ Ethanol

Scheme 2. Synthesis of the triamine **5**.

Table 1. Association Constants and $t_{1/2}$ of Decarboxylation for Receptors **1** and **2**.

Receptor	Kass (M^{-1})	$t_{1/2}$ Decarboxylation (min.)
Without receptor		110
1	$3.3x\ 10^2$	75
2	$3.8x\ 10^3$	6.0

Receptors **6** to **9** were prepared starting from the triamine **5** and the suitably substituted dichlorophosphoester and phenyl isocyanate (Scheme 3).



Scheme 3. General Synthesis of Receptors.

Kinetic results are shown in table 2. Conjugation of the nonbonding electrons of the phosphoric ester oxygen atom with a naphthalene or phenyl ring strongly reduced the decarboxylative activity in receptors **6** and **7**. The presence of a methoxy electron releasing group on the phenyl ring in **8** again increased the reaction rate.

These observations are in agreement with an interaction of the nonbonding electrons and the positively charged pyridine nitrogen ring in the transition state (Figure 3).

Table 2. $t_{1/2}$ Decarboxylation for Receptors with Changes in the Substitution of the Phosphorinane Ring.

Receptor	R	R'	$t_{1/2}$ Decarboxylation (min.)
6	2-Naphthoxy	H	10
7	Phenoxy	H	8.0
8	4-methoxyphenoxy	H	7.0
9	3-dimethylaminophenoxy	H	18
10	4-nitrophenylamino	Cl	17

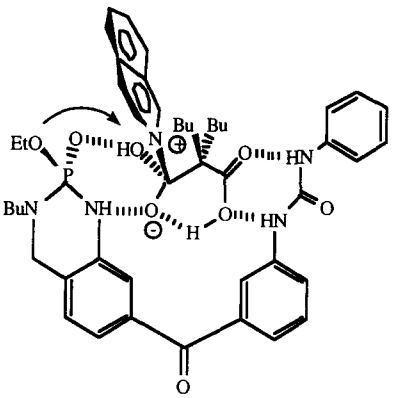


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Figure 3. Proposed Transition State Complex for Decarboxylation of DBMA and Receptor **2**.

Receptor **9** with a dimethylamino group, however, did not increase reactivity. This group is probably protonated in the reaction conditions.

A less electronegative atom such as nitrogen could interact better with the positively charged pyridinium cation and consequently increase the reactivity of malonic acid. Receptor **10** has a phosphortriamide but seems to be less efficient. This could be due to the presence of the hydrogen atom on the nitrogen, possibly introducing some steric interaction in the transition state.

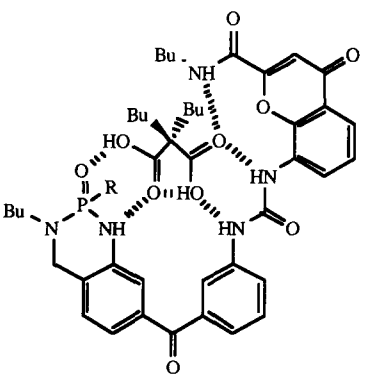
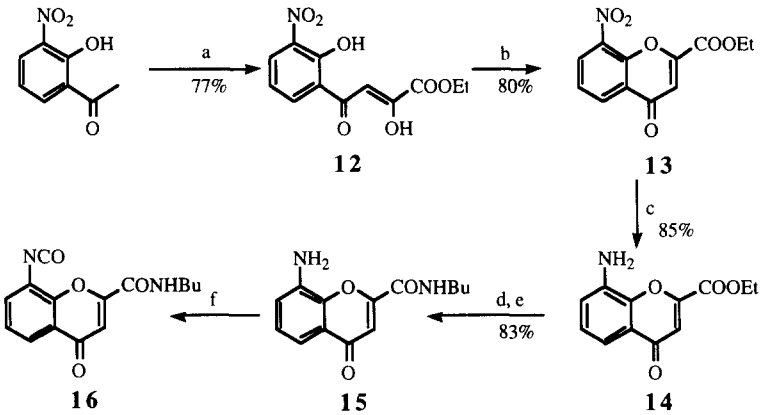


Figure 4. Complex for Receptor **11** and DBMA.

The association constants of the preceding receptors are not high and hence if the receptor is not completely associated under the working reaction conditions activity is low. A new receptor **11** was designed in which an additional hydrogen bond can be set with the malonic acid (R=OEt, Figure 4).

The synthesis was carried out as for the previous receptors by treatment with isocyanate **16**, which was prepared from 2-hydroxy-3-nitro acetophenone as shown in scheme 4.



a) EtONa/ Diethyl oxalate, b) H_2SO_4, c) $SnCl_2$/Ethanol, d) butylamine, e) acetic acid, f) phosgene.

Scheme 4. Synthesis of isocyanate **16**.

The association constant of this receptor with malonic acid is probably higher than the foregoing ones. However, broad signals in the NMR spectrum did not allow accurate measurements. The catalytic activity was not higher than those previous obtained, probably because the geometry of the transition state geometry was not improved with respect to the ground state.

Table 3. Association constants and $t_{1/2}$ of decarboxylation for receptors with different urea aromatic rings.

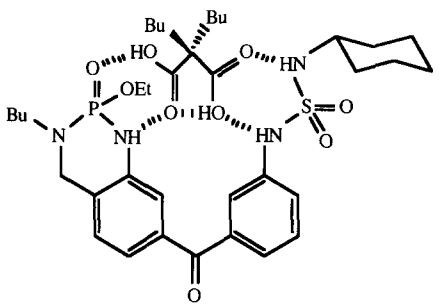
Receptor	R	R'	Kass (M^{-1})	$t_{1/2}$ Decarboxylation (min.)
11	OEt	See figure 4		5.0
17	OEt	Cl	5.0x 10^3	7.5
18	OEt	NO_2	4.6x 10^3	8.0
19	OEt	OMe	4.5x 10^3	5.0
20	OEt	See figure 5	1.3x 10^3	4.0

An interesting clue to this geometry was obtained when different substituents were included in the urea aromatic ring. Electron withdrawing groups on this aromatic ring such as chlorine or nitro should activate the urea hydrogen bonds and because they should be set with the negative carboxylate group in the transition state better activity is to be expected. These receptors **17** and **18** were obtained from reaction of the amine **5**, ethyl dichlorophosphate and the properly substituted isocyanate (Scheme 3). The association constants with dibutylmalonic acid did not change significantly with this new substitution and more accurate kinetic studies showed that in these receptors activity was surprisingly reduced (table 3).

To ensure that there was indeed a trend between the aromatic ring substituents and catalytic activity, a receptor with an electron-releasing group **19** was prepared. A methoxy group was chosen because a dimethylamino could become protonated. Once again the association constant was similar to the preceding ones (table 3). Activity, however, was slightly better than that of receptor **2** with the unsubstituted aromatic ring.

A possible explanation for these results is based on a non-ideal geometry of these receptors for transition states. Molecular models show that the tetrahedral carbon in the transition state reduces the width of the malonic acid and that a narrower cleft is necessary. If the cavity is too wide for the transition state, the urea hydrogen bond will probably be longer than in the ground state. This will handicap catalytic activity.

To reduce the width of the cleft, a new receptor **20** (Figure 5) was prepared, including a sulfurylamide instead of the urea function. The tetrahedral sulfur atom slightly reduces the size of the cleft, now providing a NH at a P=O distance of only 6.5Å instead of the former 6.9Å.



20

Figure 5. Receptor **20** and DBMA complex.

The ground state association constant was smaller than the previous ones but the catalytic activity was indeed increased. This was thus the best of these receptors and the reaction half-life was reduced to only 4 minutes (table 3).

Experimental

General. All melting points were determined with a hot plate Kofler microscope and are uncorrected. IR spectral measurements were carried out with a BOMEN-MB100FT spectrophotometer. NMR spectra were carried out with a BRUKER WP 200 SY (200 MHz). Mass spectra were performed on a VG-TS 250 (70 eV). For column chromatography silicagel Merck 60 (0.063-0.2 mm) was employed.

4-bromomethyl-3,3'-dinitrobenzophenone 3: 4-Bromomethylbenzophenone (105 g, 380 mmol) was dissolved in sulfuric acid (1000 ml.), the solution was cooled at 0°C and fuming nitric acid (37 ml., 880 mmol) was added dropwise at 10°C. The mixture was stirred for 2 hours at room temperature, added to water (4 l) and extracted with ethyl acetate. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated off. The residue was crystalized in ethanol / acetone to afford 90.2 g (65%). mp: 102 °C; ^{1}HNMR ($CDCl_3$) δ: 8.60 (t, 1H, J= 1.5 Hz), 8.50 (dd, 1H, J= 8.0, 1.5 Hz), 8.42 (d, 1H, J= 1.7 Hz), 8.13 (dd, 1H, J= 7.8, 1.5 Hz), 8.03 (dd, 1H, J= 7.8, 1.7 Hz), 7.78 (m, 2H), 4.83 (s, 2H) ppm; IR (Nujol) ν: 1674, 1612, 1532, 1265, 1080, 729 cm^{-1}; MS (m/z, %): 366 (M^+, 5%), 364 (5%), 285 (32%), 268 (50%), 150 (100%), 69 (97%).

4-Butylaminomethyl-3,3'-dinitrobenzophenone hydrochloride 4: 4-Bromomethyl-3,3'-dinitrobenzophenone (20 g, 55 mmol) was dissolved in ethyl acetate (300 ml.) and butylamine (18 g, 245 mmol)

was added. After 2 hours at room temperature, 2N HCl (200 ml.) was added and the mixture was stirred for 15 minutes. The precipitate was filtered and 15 g were obtained (76 %). mp:>300°C; ^{1}HNMR (CD_3OD) δ: 8.60 (t, 1H, J=2.0 Hz), 8.55 (d, 1H, J=1.5 Hz), 8.52 (dd, 1H, J=2.0, 8.0 Hz), 8.21 (m, 2H), 8.00 (d, 1H, J=8.0 Hz), 7.85 (t, 1H, J=8.0 Hz), 4.72 (s, 2H), 3.35 (t, 2H, J=6.0 Hz), 1.7-1.2 (m, 4H), 1.00 (t, 3H, J=7.3 Hz) ppm; IR (Nujol) ν: 3410, 1674, 1618, 1530, 918, 816, 704 cm^{-1}.

3,3'-diamino-4-butylaminomethylbenzophenone 5: 4-Butylaminomethyl-3,3'-dinitrobenzophenone hydrochloride (15 g, 42 mmol) was dissolved in a mixture of ethanol (100 ml.) and 2N HCl (100 ml.). Tin(II) chloride dihydrate (75 g, 335 mmol) was added. After 2h at room temperature, the ethanol was evaporated off and the mixture was added to a sodium hydroxide solution (80 g of NaOH in 500 ml of water). The solution was extracted with dichloromethane and the organic layer dried with anhydrous sodium sulfate and evaporated off. After chromatography, 7.7 g (68 %) of an oil were obtained. ^{1}HNMR ($CDCl_3$) δ: 7.20 (m, 7H), 3.75 (s, 2H), 3.92 (br s, 2H), 2.50 (t, 2H, J=6.0 Hz), 1.6-1.3 (m, 4H), 0.95 (t, 3H, J=6.2 Hz) ppm; ^{13}CNMR ($CDCl_3$): 197 (1C,C), 146.7 (1C,C), 146.4 (1C,C), 138.9 (1C,C), 137.6 (1C,C), 129.2 (1C,CH), 128.7 (1C,CH), 128.5 (1C,C), 120.1 (1C,CH), 119.6 (1C,CH), 118.5 (1C,CH), 116.5 (1C,CH), 115.7 (1C,CH), 52.7 (1C,CH_2), 48.9 (1C,CH_2), 31.95 (1C,CH_2), 20.3 (1C,CH_2), 13.83 (1C,CH_3); IR ν: 1670, 1649, 1559, 1454, 1431, 1321, 1107, 874, 791 cm^{-1}; MS (m/z, %): 297 (M^+, 25%), 240 (60%), 225 (50%), 120 (30%), 92 (30%), 69 (100%).

General procedure for receptors: 3,3'-Diamino-4-butylaminomethyl benzophenone **5** (0.5 g, 1.7 mmol) was dissolved in dichloromethane (5 ml). triethylamine (0.5 ml.) was added plus the corresponding dichlorophosphate (1.7 mmol). The reaction was stirred at room temperature for 2 days and the isocyanate was added (1.7 mmol). After 2 hours the solvent was evaporated and the mixture was chromatographed on silica gel. The compound was crystalized with dichloromethane / hexane.

1-[3-(3-Butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-3-phenyl urea 2: by the general procedure with ethyl dichlorophosphate and phenyl isocyanate. 0.6 g were obtained (70%). mp: 125°C; ^{1}HNMR ($CDCl_3$) δ: 7.75 (d, 1H, J=7.4 Hz), 7.61 (s, 1H), 7.4-6.6 (m, 10H), 4.34 (dd, 1H, J=8.3, 16.0 Hz), 4.0 (m, 3H), 3.2-1.7 (m, 2H), 1.5 (m, 2H), 1.3 (m, 2H), 1.28 (t, 3H, J=7.3 Hz), 0.84 (t, 3H, J=7.2 Hz); ^{13}CNMR ($CDCl_3$) δ: 195.9 (1C, C), 153.61 (1C, C), 140.10 (1C,C), 139.49 (1C, C), 138.69 (1C, C), 137.6 (1C, C), 137.3 (1C, C), 128.75 (2C, CH), 127.18 (1C, C), 126.44 (1C, CH), 124.22 (1C, CH), 123.29 (1C, CH), 122.75 (1C, CH), 120.16 (1C, CH), 119.38 (1C, CH), 118.71 (2C, CH), 118.71 (1C, CH), 117.74 (1C, CH), 62.38 (1C, CH_2), 49.49 (1C, CH_2), 47.02 (1C, CH_2), 30.84 (1C, CH_2), 19.76 (1C, CH_2), 16.04 (1C, CH_3), 13.61 (1C, CH_3); IR ν: 3281, 1724, 1642, 1593, 1557, 1302, 1246, 1215, 1196, 1034, 974, 748 cm^{-1}; MS (m/z, %): 413 (M^+-C_6H_6N, 10 %), 370 (13%), 212 (10%), 119 (50%), 93 (100%).

1-[3-(3-Butyl-2-oxo-2-phenoxy-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-3-phenyl urea 7: by the general procedure with phenyl dichlorophosphate and phenyl isocyanate. 0.54 g were obtained (58%). mp: 217°C; ^{1}HNMR ($CDCl_3$) δ: 8.5-6.5 (m, 17H), 4.45 (dd, 1H, J=6.2, 15.9 Hz), 4.04 (dd, 1H, J=23, 15.9Hz), 3.16 (m, 2H), 1.52 (m, 2H), 1.24 (m, 2H), 0.79 (t, 3H, J=7.3 Hz); IR ν: 3350, 1693, 1655, 1599, 1550, 1307, 1236, 1197, 964, 929, 765, 748 cm^{-1}; MS (m/z, %): 461 (M^+-C6H6N, 60%), 435 (45%), 418 (100%), 392 (85%), 119 (55%), 93 (95%).

1-{3-[3-Butyl-2-(naphtalen-2-yloxy)-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl]-phenyl}-3-phenyl urea 6: by the general procedure with naphthyl dichlorophosphate and phenyl isocyanate. 0.70 g were obtained (67%). mp: 132°C; ^{1}HNMR ($CDCl_3$) δ: 8.0-6.8 (m, 19H), 4.42 (dd, 1H, J=7.0, 16.0 Hz), 4.10 (dd, 1H, J=24,16.0 Hz), 3.2 (m, 2H), 1.5 (m, 2H), 1.2 (m, 2H), 0.79 (t, 3H, J=7.2Hz); IR ν: 1653, 1597, 1548, 1307, 1244, 1213, 1157, 966, 927,

750, 659 cm^{-1}; MS (m/z, %): 532 (M^+- C_6H_6N, 13%), 212 (10%), 144 (100%), 115 (55%), 93 (80%), 73 (50%).

1-{3-[3-Butyl-2-(4-methoxyphenyloxy)-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl]-phenyl}-3-phenyl urea 8: by the general procedure with p-methoxyphenyl dichlorophosphate and phenyl isocyanate. 0.72 g were obtained (74%). mp: 152°C; ^{1}HNMR ($CDCl_3$) δ: 7.78 (d, 1H, J=7.2 Hz), 7.59 (d, 1H, J=6.9 Hz), 7.57 (s, 1H), 7.41 (s, 1H), 7.4-6.8 (m, 10H), 6.67 (d, 2H, J=7.8 Hz), 4.45 (dd, 1H, J= 6.6, 16 Hz), 4.06 (dd, 1H, J=16, 22 Hz), 3.63 (s, 3H), 3.2 (m, 2H), 1.55 (m, 2H), 1.3 (m, 2H), 0.77 (t, 3H, J=6.2 Hz); IR ν: 3346, 1712, 1655, 1641, 1591, 1548, 1504, 1305, 1226, 1242, 1201, 920, 906, 758, 721 cm^{-1}; MS (m/z, %): 491 (M+-C6H6N, 6%), 212 (10%), 119 (62%), 93 (100%).

1-{3-[3-Butyl-2-(3-dimethylaminophenyloxy)-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl]-phenyl}-3-phenyl urea 9: by the general procedure with m-dimethylaminophenyl dichlorophosphate and p-chlorophenyl isocyanate. 0.43 g were obtained (44%). mp: 142°C; ^{1}HNMR ($CDCl_3$) δ: 8.0-6.2 (m, 16H), 4.36 (dd, 1H, J=6.9, 15.3 Hz), 4.10 (dd, 1H, J=24,15.3 Hz), 3.7 (m, 2H), 2.8 (s, 6H), 1.5 (m, 2H), 1.2 (m, 2H), 0.79 (t, 3H, J=7.2 Hz); IR ν: 3540, 1720, 1660, 1549, 1312, 1240, 1200, 1158, 927, 751, 659 cm^{-1}.

1-{3-[3-Butyl-2-(4-nitrophenylamino)-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl]-phenyl}-3-(4-chlorophenyl) urea 10: by the general procedure with p-nitrophenyl dichlorophosphoramide and p-chlorophenyl isocyanate. 0.62 g were obtained (62%). mp: 192°C; ^{1}HNMR (CD_3OD) δ: 8.25 (d, 2H, J=9.2 Hz), 8.12 (s, 1H), 7.9-7.3 (m, 12H), 4.6-4.2 (m, 2H), 3.6-3.2 (m, 2H), 1.8-1.7 (m, 2H), 1.07 (t, 3H, J=7.2 Hz); ^{13}CNMR (CD_3OD) δ: 197.3 (1C, C), 155.5 (1C, C), 143.5 (1C, C), 143.0 (1C, C), 141.8 (1C, C), 140.6 (1C, C), 139.1 (1C, C), 138.4 (1C,C), 129.7 (1C, C), 129,6 (2C, CH), 129.5 (2C, CH), 128.6 (1C, C), 127.7 (1C, CH), 124.8 (1C, CH), 123.8 (1C, CH), 123.7 (1C, CH), 123.6 (1C, CH), 121.4 (2C, CH), 120.9 (1C, CH), 120.2 (2C, CH), 119.0 (1C, CH), 118.2 (1C, C), 50.0 (1C, CH_2), 47.5 (1C, CH_2), 31.6 (1C, CH_2), 20.7 (1C, CH_2), 14.0 (1C, CH_3); IR ν: 3252, 1703, 1649, 1595, 1549, 1341, 1300, 1213, 1182, 1113, 1051, 936, 824, 725 cm-1.

8-{3-[3-(3-butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-ureido}-1-oxo-*4H*-chromene-2-carboxylic acid butylamide 11: by the general procedure with ethyl dichlorophosphate and isocyanate **16**. This isocyanate was obtained by treatment of the amine **15** (0.5 g, 1.7 mmol) in dichloromethane (5 ml) with phosgene in toluene (20%) (4 ml, 8 mmol) for 5 minutes. Then removed the solvent under vacuum. 0.55 g were obtained (48%). mp: 219 °C; ^{1}HNMR (CD_3OD) δ: 8.40 (d, 1H, J=8.0 Hz), 7.90 (s, 1H), 7.70 (m, 2H), 7.37 (m, 3H), 7.20 (m, 3H), 6.90 (s, 1H), 4.40 (dd, 1H, J=12.2, 22.2 Hz), 4.20 (dd, 1H, J=20.0, 22.2 Hz), 4.00 (m, 2H), 3.20 (m, 4H), 1.45 (m, 8H), 1.25 (t, 3H, J=7.0), 0.89 (t, 6H, J=7.0) ppm; IR (Nujol) ν: 3273, 1719, 1684, 1661, 1557, 1287, 1196, 1040, 968, 814, 752 cm^{-1}; MS (m/z, %): 413 (M^+-$C_{14}H_{14}N_2O_3$, 20%), 388 (30%), 371 (50%), 345 (60%), 260 (100%), 245 (60%), 130 (100%), 104 (100%), 77 (60%).

2-hydroxy-4-(2-hydroxy-3-nitrophenyl)-4-oxo-but-2-enoic acid ethyl ester 12: Sodium (0.30 g, 1.3 mmol) was dissolved in absolute ethanol (12 ml). Diethyl oxalate (1.2 g, 0.9 mmol) and 3-hydroxy-2-nitro acetophenone (0.50 g, 0.30 mmol) were added. The solution was refluxed for 20 minutes, evaporating the solvent to 5 ml, and this residue was added to 2N HCl (50 ml). The precipitate was filtered and dried and 0.6 g were obtained (77 %). mp: 74 °C; ^{1}HNMR ($CDCl_3$) δ: 8.31 (dd, 1H, J=8.3, 1.7 Hz), 8.21 (dd, 1H, J=8.3, 1.7 Hz), 7.34 (1H, s), 7.13 (t, 1H, J=8.3 Hz), 4.42 (q, 2H, J=7.1 Hz), 1.42 (t, 3H, J=7.1 Hz) ppm; IR (Nujol) ν: 3500, 1724, 1628, 1576, 1526, 1464, 1275, 1167, 1099, 1022, 910, 856, 779, 748, 667 cm^{-1}; MS (m/z, %): 281 (M^+, 15%), 208 (98%), 166 (100%), 149 (95%), 120 (92%), 91 (50%), 69 (92%).

8-nitro-4-oxo-*4H*-chromene-2-carboxylic acid ethyl ester 13: Compound **12** (0.8 g, 2.8 mmol) was dissolved in sulfuric acid (8 ml) and heated at 60°C for 5 minutes. The mixture was added to water (40 ml) and the precipitate was filtered. 0.6 g were obtained (80%). mp: 118 °C; ^{1}HNMR ($CDCl_3$) δ: 8.49 (dd, 1H, J=7.9, 1.7 Hz), 8.39 (dd, 1H, J=7.9, 1.7 Hz), 7.58 (t, 1H, J=7.9 Hz), 7.21 (s, 1H), 4.49 (q, 2H, J=7.1 Hz), 1.45 (t, 3H, J=7.1 Hz) ppm; IR (Nujol) ν: 1740, 1667, 1615, 1532, 1209, 1101, 899, 849, 777, 743 cm^{-1}; MS (m/z, %): 263 (M^+, 42%), 235 (20%), 218 (15%), 205 (18%), 191 (20%), 149 (12%), 137 (18%), 119 (28%), 81 (57%), 69 (100%).

8-amino-4-oxo-*4H*-chromene-2-carboxylic acid ethyl ester 14: Compound **13** (0.40 g, 1.5 mmol) was dissolved in a mixture of HCl 2N (4 ml) and ethanol (4 ml). Tin (II) chloride dihydrate (1.5 g, 6.0 mmol) was added. The reaction was heated up to complete dissolution. The ethanol was vacuum-distilled and the mixture added to sodium carbonate (10 g) in ethyl acetate. The precipitate was separated and the filtrate is dried with sodium sulfate and evaporated. 0.3 g of compound **14** were obtained (85%). mp: 156 °C; ^{1}HNMR ($CDCl_3$) δ: 7.52 (dd, 1H, J=7.9, 1.5 Hz), 7.22 (t, 1H, J=7.9 Hz), 7.08 (s, 1H), 7.05 (dd, 1H, J= 7.9, 1.5 Hz), 4.46 (q, 2H, J=7.1 Hz), 4.29 (s, 2H), 1.43 (t, 3H, J=7.1 Hz) ppm; IR (Nujol) ν: 3339, 1723, 1670, 1600, 1582, 1302, 1267, 1206, 1022, 866, 775, 735 cm^{-1}; MS (m/z, %): 233 (M^+, 80%), 205 (65%), 149 (20%), 135 (31%), 81 (41%), 69 (100%).

8-amino-4-oxo-*4H*-chromene-2-carboxylic acid butylamide 15: The amine **14** (0.70 g, 3.0 mmol) was dissolved in butylamine (1 ml) and heated at 60°C for 10 minutes. The solvent was vacuum-distilled and acetic acid (1 ml) was added. The mixture was heated for 10 minutes again and added to water (20 ml). The precipitate was filtered and 0.65 g were obtained (83%). mp: 216°C; ^{1}HNMR ($CDCl_3$) δ: 7.57 (dd, 1H, J=8.2, 1.3 Hz), 7.23 (t, 1H, J=8.2 Hz), 7.08 (dd, 1H, J=8.2, 1.3 Hz), 7.09 (s, 1H), 3.48 (q, 2H, J=7.6 Hz), 1.8-1.5 (m, 2H), 1.5-1.3 (m, 2H), 0.96 (t, 3H, J=7.5 Hz); IR (Nujol) ν: 3252, 1703, 1649, 1595, 1549, 1341, 1300, 1213, 1182, 1113, 1051, 1015, 936, 824, 725 cm^{-1}.

1-[3-(3-Butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-3-(4-chlorophenyl) urea 17: by the general procedure with ethyl dichlorophosphate and p-chlorophenyl isocyanate. 0.56 g were obtained (61%). mp: 190 °C; ^{1}HNMR ($CDCl_3$) δ: 8.40 (s, 1H), 8.10 (s, 1H), 7.20 (m, 9H), 4.30 (dd, 1H, J=7.4, 16 Hz), 4.03 (m, 3H), 3.2-2.8 (m, 2H), 1.50-1.2 (m, 4H), 1.28 (t, 3H, J=7.1 Hz), 0.81 (t, 3H, J=7.0 Hz) ppm; IR (Nujol) ν: 3295, 1715, 1638, 1595, 1539, 1308, 1194, 1011, 964, 828, 754 cm^{-1}; MS (m/z, %): 413 (M^+-ClC_6H_4NH, 5%), 387 (8%), 370 (12%), 345 (12%), 153 (85%), 127 (100%), 90 (32%).

1-[3-(3-Butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-3-(4-nitrophenyl) urea 18: by general procedure with ethyl dichlorophosphate and p-nitrophenyl isocyanate. 0.74 g were obtained (80%). mp: 135 °C; ^{1}HNMR ($CDCl_3$) δ: 8.88 (s, 1H), 8.67 (s, 1H), 8.05 (d, 2H, J=9.0 Hz), 7.30 (m, 7H), 4.45 (dd, 1H, J=7.9, 16 Hz), 4.15 (m, 3H), 3.3-2.9 (m, 2H), 1.7-1.2 (m, 4H), 1.35 (t, 3H, J=7.3 Hz), 0.85 (t, 3H, J=7 Hz) ppm; IR (Nujol) ν: 3291, 1724, 1645, 1595, 1561, 1508, 1329, 1192, 1177, 1111, 1034, 968, 853, 750, 725 cm^{-1}; MS (m/z, %): 551 (M^+, 2%), 413 (16%), 387 (45%), 344 (100%), 138 (37%), 92 (48%).

1-[3-(3-Butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl]-3-(4-methoxy phenyl) urea 19: by the general procedure with ethyl dichlorophosphate and p-methoxyphenyl isocyanate. 0.60 g were obtained (67%). mp: 106 °C; ^{1}HNMR ($CDCl_3$) δ: 8.10 (s, 1H), 7.80 (s, 1H), 7.45 (s, 1H), 7.2 (m, 6H), 6.81 (d, 2H, J=8.0 Hz), 4.45 (dd, 1H, J=8.0, 16 Hz), 4.1 (m, 3H), 3.74 (s, 3H), 3.08 (m, 2H), 1.50 (m, 2H), 1.35 (m, 5H), 0.90 (t, 3H, J=7.0 Hz) ppm; IR (Nujol) ν: 3256, 1709, 1640, 1591, 1561, 1512, 1458, 1377, 1302, 1213, 974, 949, 750 cm^{-1}; MS

(m/z, %): 413 (M+-$CH_3OC_6H_4NH$-, 10%), 388 (11%), 370 (32%), 149 (38%), 123 (52%), 108 (100%), 80 (85%).

1-[3-(3-Butyl-2-ethoxy-2-oxo-1,2,3,4-tetrahydro-benzo[1,3,2]diazaphosphonine-7-carbonyl)-phenyl] cyclohexyl sulfurilamine 20: by the general procedure with ethyl dichlorophosphate and N-cyclohexyl sulfamoyl chloride. 0.54 g were obtained (59%). mp: 120 °C; ^{1}HNMR ($CDCl_3$) δ: 7.3 (m, 7H), 4.43 (dd, 1H, J=6, 16 Hz), 4.1 (m, 3H), 3.0 (m, 3H), 1.3 (m, 17H), 0.9 (t, 3H, J=7 Hz) ppm; IR (Nujol) v: 3289, 1653, 1605, 1586, 1458, 1377, 1304, 1227, 1154, 1034 cm^{-1}; MS (m/z, %): 548 (M+, 10%), 387 (50%), 344 (100%), 330 (10%), 217 (45%), 98 (50%), 83 (60%).

Dibutylmalonic acid decarboxylation studies: Isoquinoline (0.1168 g, 0.9 mmol), nitrobenzene (3.2032 g, 26 mmol) and dibutylmalonic acid (4.5450 g, 21 mmol) were dissolved in ether (50 ml). A part of the solution (2 ml) was added to 0.06 mmol of the different receptors. The ether was vacuum-distilled and the remaining oil was heated to 125°C in a thermostatted oil bath. The formation of CO_2 was followed by a gas-burette until gas formation ceased. The $t_{1/2}$ was evaluated by interpolation in the kinetic plot.

Association constant measurements: ^{1}HNMR spectra were recorded from ten samples at a constant host concentration (10^{-3} M) and different amounts of guest (between 0 and 10^{-3} M). Non-linear curve fitting from the chemical shifts against the guest concentration obtained in the experiment affords the value of the association constant.

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References and notes:

1. a) Snyder, H. R.; Shekleton, J.F.; Lewis, C. D., *J. Am. Chem. Soc.*, **1945**, *67*, 310. b) Snyder, H. R.; Howe, E. E.; Cannon, G.W.; Nyman, M. A., *J. Am. Chem. Soc.*, **1943**, *65*, 2211. c) Goldsmith, D.; Tishler, M., *J. Am. Chem. Soc.*, **1946**, *68*, 144.
2. Barton, D.; Ollis, W.D., *Comprehensive Organic Chemistry, "The synthesis and reactions of organic compounds"*, vol. 5, **1979**.
3. a) García-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S. J.; Hamilton, A. D., *J. Am. Chem Soc.*, **1990** *112*, 7393. b) Rebek Jr., J.; Nemeth, D., Ballester, P.; Lin, F.-T., *J. Am. Chem. Soc.*, **1987**, *109*, 3474. c) Grande, M.; Raposo, C.; Sanz, M. J.; Mussons, M. L.; Crego, M. Moran, J. R., *An. de Quim.*, **1993**, *89*, 617. d) Fenniri, H; Lehn, J.M.; Marquis-Rigault, A., *Angew. Chem. Int. Ed. Engl.*, **1996**, *25*, 337.
4. Eberson, L., in "*The chemistry of Carboxylic Acids and Esters*", Patai, S., Ed., Wiley- Interscience, New York, **1969**, 211.
5. Pauling, L., *Chem. Eng. News*, **1946**, *24*, 1375.
6. Raposo, C.; Crego, M.; Partearroyo, A.; Mussons, M. L.; Caballero, M. C.; Morán, J. R., *Tetrahedron Lett.*, **1992**, *34*, 1995.
7. Crark, L., in *The Chemistry of Carboxylic Acids and Esters*, Patai, S., Ed., Wiley- Interscience, New York, **1969**, 589.
8. Corey, E. J.; Fraenkel, G., *J. Am. Chem. Soc.*, **1953**, *75*, 1168.

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