Pergamon

Tetrahedron Letters, Vol. 37, No. 9, pp. 1485-1488, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00045-7

Cleft Type Receptors for Butenolides Based on Chromenone Derivatives

César Raposo, Marta Almaraz, Nieves Pérez, Mercedes Martín, Volker Weinrich, Manuel Grande, Mª Cruz Caballero, and Joaquín R. Morán

Departamento de Química Orgánica, Universidad de Salamanca, Plaza de los Caídos 1-5, Salamanca, 37008 Spain

Abstract: A chromenone building block is suitable for the preparation of H-bonding lactone receptors. Combination of this fragment with a second chromenone provides a new cleft suitable for strongly association of γ-hydroxymethyl-γ-lactones.

But-2-enolides display broad chemical reactivity in nucleophilic addition[1] or as dienophiles in electrocyclic reactions[2]. Such molecules also present strong biological activity[3]. Butenolides are therefore interesting targets for Molecular Recognition. However, to our knowledge, so far very few receptors have been found to be able to associate lactones[4].

Study of molecular models shows that chromenone fragments, as in receptor **5**, may be excellent candidates for lactones **1-3**, providing the necessary geometry to set three linear H-bonds (Fig.1).

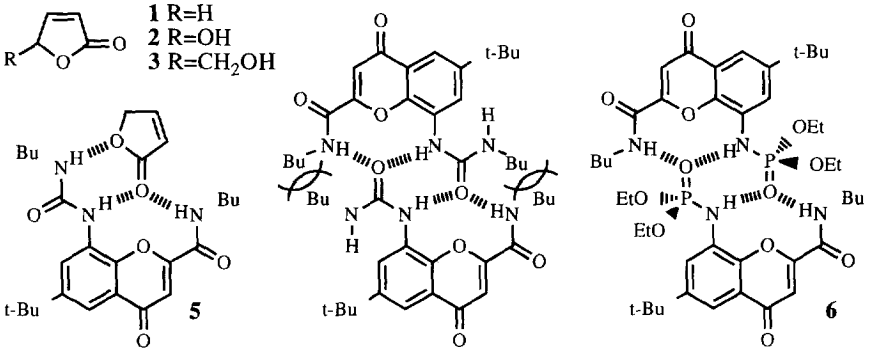
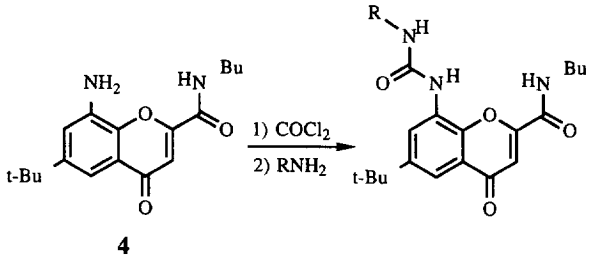


Figure 1. Guests, complex between receptor **5** and lactone **1** and proposed dimers for receptors **5** and **6**

Receptors **5** and **6** were prepared easily starting from the aminochromane **4**[5] as shown in schemes 1 and 2, respectively. Receptor **5** (m.p.= 122-126°C) is essentially unable to bind butyrolactone in $CDCl_3$, probably because **5** shows a self-complementary structure which leads to dimerization in this solvent. A value of Kd= 5.0×10^2 M^{-1} for the dimerization is afforded in ^{1}HNMR experiments[6]. Scruting of molecular models suggests a

certain degree of steric hindrance between the urea and amide butyl chains of different molecules (Fig. 1). This fact is also supported because a similar compound **6** (m.p.= 154-156°C), in which the urea has been changed into a phosphoramide group, presents a stronger self-association, which ^{1}HNMR studies can only evaluate above 10^4 M^{-1}. In this case, the tetrahedral geometry of the phosphorus atom prevents interference between the alkyl chains in the dimer units.

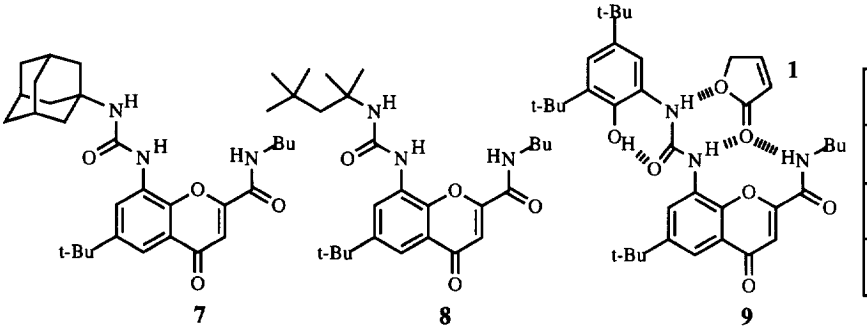


4

Receptor	Amine	Yield
5	Butylamine	90%
7	1-adamantylamine	85%
8	t-Octylamine	95%
9	3,5-di-t-butyl-2-hydroxyaniline	82%
10	6-amino-2-pycoline	74%

Scheme 1. Synthesis of urea-type receptors for lactones **1** and **2**

The presence of steric effects in the receptor **5** dimer should allow easy preparation of receptors with lower self-association (Scheme 1). The bulky adamantyl group in receptor **7** (Fig. 2, m.p.= 222-224°C) collides in its dimer with the butyl chain, reducing the self-association to Kd=1.5x10^2 M^{-1}, and a similar effect is obtained for the t-octyl derivative **8** (m.p.= 178-180°C), which shows Kd= 1.0x10^2 M^{-1}.



7 **8** **9**

Receptor	Kd (M^{-1})
7	1.5x10^2
8	1.0x10^2
9	3.0x10^1

Figure 2. Structures for receptors **7** to **9** and their self-association constants

The best results to avoid self-association are obtained when a smaller steric effect is combined with an intramolecular H-bond, as in receptor **9** (m.p.= 154-156°C). In this case, self-association is reduced to Kd= 3.0x10^1 M^{-1}. This small dimerization constant allows one to study the association constant with 2-(*5H*)-furanone **1** (Fig. 2). The association constant[7] was measured in diluted solution (3x10^{-3} M) with a large excess of the butenolide **1** to prevent a strong interference by the dimerization process. Under these conditions, a Kass= 3.0x10^1 M^{-1} was obtained. No change was obtained for this association constant when dimer formation was taken into account[8].

Hydroxylactones such as 5-hydroxy-2-(*5H*)-furanone **2** offer the possibility of setting more H-bonds in the complex and therefore could provide higher association constants. Since aminopyridines are known to be good hydrogen bond acceptors[9], one of these units was included in receptor **10** (m.p.= 216-218°C) to provide a fourth hydrogen bond with the hydroxyl group. However, both the dimer formation (Kd= 1.6x10^2 M^{-1}) and the lactone **2** association constant (Kass= 3.2x10^1 M^{-1}) are surprisingly low for this receptor **10**, probably due to the presence of a competing six membered ring intramolecular hydrogen bond (Fig. 3).

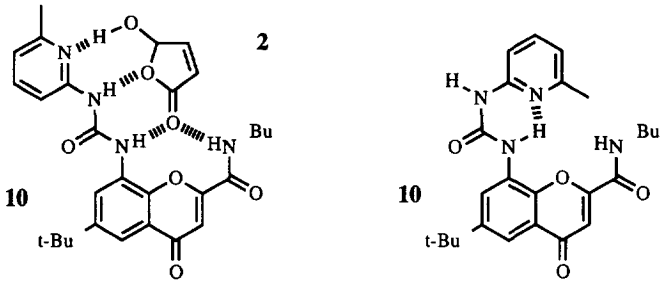
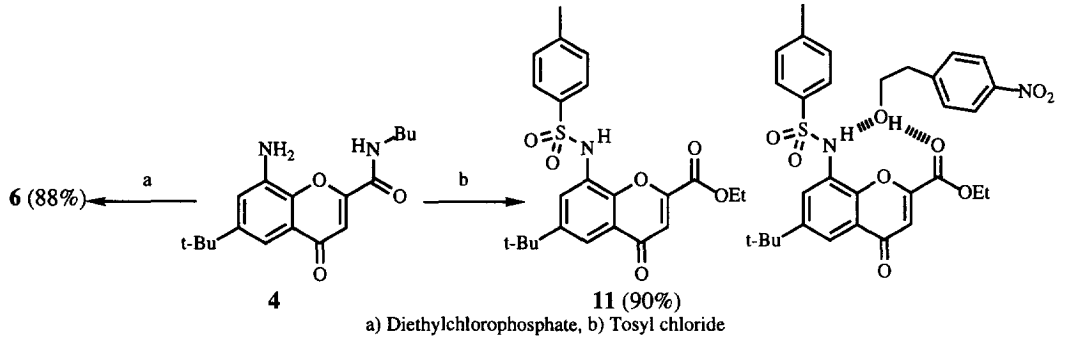


Figure 3. Proposed structures for the complex of receptor **10** with hydroxylactone **2** and its possible intramolecular H-bond

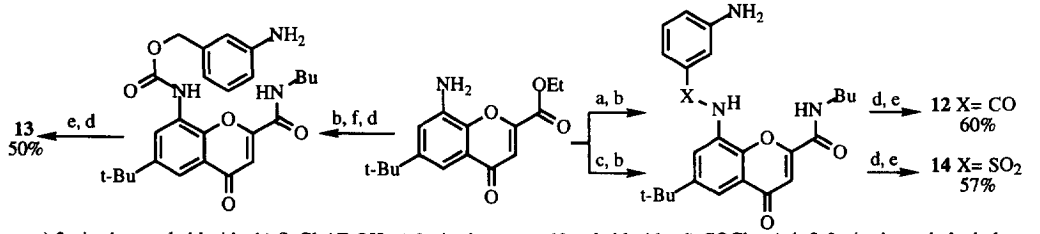
A chromenone unit is also able to associate alcohols because two strong linear hydrogen bonds can be set with the hydroxyl group. For example, the association constant for the sulfonamide **11** (prepared as shown in scheme 2, m.p.= 144-146°C) and the crystalline 2-(4-nitrophenyl)-ethanol is Kass= 9.0 M^{-1}.



a) Diethylchlorophosphate, b) Tosyl chloride

Scheme 2. Synthesis of receptors **6** and **11** and the proposed complex for receptor **11** and 2-(4-nitrophenyl)-ethanol

CPK molecular models suggest three readily available spacers to link both lactone and hydroxyl binding sites of dichromenone receptors **12-14** in order to fit 5-hydroxymethyl-2-(*5H*)-furanone **3** (Fig. 4). The greater distance between the OH group and the lactone compared to lactone **2** in this guest allows an easier design of receptors lacking intramolecular hydrogen bonds. Easy preparation of these receptors was carried out as shown in scheme 3.

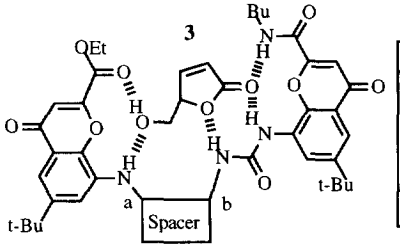


a) 3-nitrobenzoyl chloride, b) $SnCl_2$/ EtOH, c) 3-nitrobenzenesulfonyl chloride, d) $COCl_2$, e) **4**, f) 3-nitrobenzyl alcohol

Scheme 3. Preparation of compounds **12** to **14**

The benzoic unit of receptor **12** (m.p.= 186-190°C) is the most rigid spacer. However, it shows the worst fit with hydroxylactone **3** and consequently the complex has poor stability, with Kass= 8.5×10^1 M^{-1}. The flexible spacer in receptor **13** (m.p.= 224-226°C) allows a good model fit with guest **3**, although many rotational degrees of freedom must be frozen in the complex, leading to poor cooperativity between both binding sites. In this case,

an apparent association constant can be measured Kass= $1.3x10^2$ M^{-1}. Correction due to dimer formation (Kd= $7.0x10^2$ M^{-1}) leads to a small increase up to Kass= $1.7x10^2$ M^{-1}.



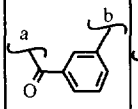
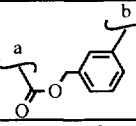
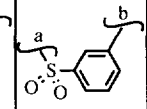
Receptor	12	13	14
Spacer			
Kass (M^{-1})	$8.5x10^1$	$1.7x10^2$	$6.7x10^3$

Figure 4. Association constants and proposed structure for the complexes of receptors **12** to **14** with hydroxylactone **3**

A phenylsulfonyl spacer provides the best compromise between rigidity and fit in receptor **14** (m.p.= 178-182°C). This compound again shows self-association with a Kd= $5.0x10^2$ M^{-1}. The association constant with hydroxylactone **3** measured in a diluted solution ($3x10^{-4}$ M) to prevent strong dimer interference, showed Kass= $4.2x10^3$ M^{-1}. Correction of the data due to the small amount of dimer leads to Kass= $6.7x10^3$ M^{-1}. This high association constant indicates that cooperativity between both binding sites is good, making further work on these lactone receptors promising.

Acknowledgments: We thank the "Dirección General de Investigación Científica y Técnica" (DGICYT Grant PB 92-0286) for its support of this work. C. R. also thanks the MEC for a fellowship.

References and notes

1 a) Feringa, B. L.; de Lange, B., *Tetrahedron Lett.*, **1988**, *29*, 1303. b) Faber, W. S.; Kok, J.; de Lange, B.; Feringa, B. L., *Tetrahedron*, **1994**, *50*, 4775.

2 a) Tanaka, M.; Tomioka, K.; Koga, K., *Tetrahedron Lett.*, **1985**, *26*, 3035. b) Ortuño, R. M.; Corbera, J.; Font, J., *Tetrahedron Lett.*, **1986**, *27*, 1081. c) Mann, J.; Thomas, A., *Tetrahedron Lett.*, **1986**, *27*, 3533. d) Ortuño, R. M.; Bigorra, J.; Font, J., *Tetrahedron*, **1987**, *43*, 2199.

3 a) Jones, J. B.; Barker, J. N., *Can. J. Chem.*, **1970**, *48*, 1574. b) Woedenbag, H. J.; Merfort, I.; Passreiter, C. M.; Schmidt, T. J.; Willuhn, G.; Unden, W.; Pras, N.; Kampinga, H. H.; Konings, A. W. T., *Planta Med.*, **1994**, *60*, 434.

4 a) Alcázar, V.; Morán, J. R.; de Mendoza, J., *Tetrahedron Lett.*, **1995**, *36*, 3941. b) Bell, D. A.; Anslyn, E. V., *J. Org. Chem.*, **1994**, *59*, 512. c) Raposo, C.; Almaraz, M.; Crego, M.; Mussons, M. L.; Pérez, N.; Caballero, M. C.; Morán, J. R., *Tetrahedron Lett.*, **1994**, *35*, 7065.

5 Raposo, C.; Pérez, N.; Almaraz, M.; Mussons, M. L.; Caballero, M. C.; Morán, J. R., *Tetrahedron Lett.*, **1995**, *36*, 3255.

6 Dimerization constants were measured following proton shifts in dilution studies (concentrations from 10^{-2} M to 10^{-4} M) in $CDCl_3$ at 293K. A Monte-Carlo non-linear curve-fitting program was used to evaluate the self-association.

7 Association constants were measured in $CDCl_3$ at 293K. Samples a with constant concentration of host (variable from $5x10^{-3}$ to $3x10^{-4}$ M, depending on the association constant range) and an increasing concentration of guest were prepared for ^{1}HNMR spectra. A Monte-Carlo non-linear curve-fitting program was used to calculate the value of the constant. A similar program allows correction due to self association.

8 Crego, M.; Partearroyo, A.; Raposo, C.; Mussons, M. L.; López, J. L.; Alcázar, V.; Caballero, M. C.; Morán, J. R., *Tetrahedron Lett.*, **1994**, *35*, 1435.

9 a) Chang, S. K.; Fan, E.; Van Engen, D.; Hamilton, A. D., *J. Am. Chem. Soc.*, **1991**, *113*, 7640. b) Tecilla, P.; Jubian, V.; Hamilton, A. D., *Tetrahedron*, **1995**, *51*, 435.

(*Received in UK* 8 *November* 1995; *revised* 7 *December* 1995; *accepted* 8 *January* 1996)