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Conformational analysis of carboxyphenylglycine (CPG) derivatives: insight into bioactive and bioselective conformations of group-I mGluRs antagonists

Antonio Macchiarulo, Antonio Entrena Guadix [1], Gabriele Costantino *

Dipartimento di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 1 06127 Perugia, Italy

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Abstract

A series of carboxyphenylglycine (CPG) derivatives, endowed with diverse activity and selectivity at metabotropic glutamate receptors (mGluRs), were subjected to an extensive conformational analysis by employing molecular mechanics, semiempirical and ab initio methods. The comparison of the conformational profiles of active and inactive CPGs suggests a possible bioactive conformation characterized by a value of 10° for the N–C_α–C^1_{Ph}–C^2_{Ph} angle, with this conformation characterized by ammonium group of the amino acid moiety lying on the plane defined by the aromatic ring.

Keywords: Metabotropic glutamate receptors; Antagonists; Conformational analysis; Bioactive conformations

1. Introduction

Metabotropic glutamate receptors (mGluRs) constitute a heterogeneous family of G-protein coupled receptors that are sensitive to L-glutamic acid (**1**, Chart 1), the principal excitatory neurotransmitter in the central nervous system (CNS) of vertebrates. At least eight genes encode molecularly diverse mGluR subtypes, named mGluR1 to mGluR8. These have been classified into three groups on the basis of sequence homology, coupling to intracellular systems, and agonist/antagonist pharmacology [1]. Thus, group I includes the prevalently postsynaptically localized mGluR1 and mGluR5 subtypes. Both mGluR1 and mGluR5 are involved in the propagation of neurodegenerative processes and group I antagonists have been proven effective in a variety of models of excitotoxicity. Group II is composed of mGluR2 and mGluR3 subtypes. While neuronal group II subtypes are localized on the presynaptic densities where they control the release of glutamic acid, the mGluR3 subtype also has a glial localization, where it exerts a neuroprotective effect through the production of neurotrophic factors. Group III includes mGluR4, mGluR6, mGluR7 and mGluR8. With the exception of mGluR6, which is exclusively expressed by ON bipolar cells on the retina, group III subtypes are prevalently expressed at presynaptic levels, where they control the release of neurotransmitters, glutamic acid and GABA in particular.

Group I mGluRs, and mGluR1 in particular, are currently the object of an intense research activity, mainly due to their involvement in a number of processes leading to excitotoxic neuronal death after ischemia [2], and several data indicate that mGluR1 antagonists may have a sustained potential as neuroprotective agents [3].

The class of carboxyphenylglycines (CPGs, chart 1), first reported by Watkins et al. [4], has constituted the exclusive source for group I mGluRs antagonists for many years. CPGs, however, are generally endowed with only a moderate potency and poor selectivity and only recently substituted CPGs have been reported to interact selectively with mGluR1 subtypes (LY367385, **6**) [5] or mGluR5 (CHPG, **9**) [6].

Despite the profound impact that CPGs have had in the pharmacological characterization of mGluRs, a comprehensive study on the structural feature of CPGs

* Corresponding author.

E-mail address: gabri@iris.chimfarm.unipg.it (G. Costantino).

[1] On leave from Departamento de Quimica Organica, Universidad de Granada, Granada, Spain.

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that may affect potency and selectivity is still lacking. We have previously reported the hypothesis that CPGs behave as mGluR1 antagonists by blocking the transition between the open and the functionally active closed form of the amino-terminal domain (ATD) of mGluR1, and we have also given explanations to why some CPG derivatives, namely, 3-hydroxyphenylglycine or 3,5-dihydroxyphenylglycine (DHPG, **10**) behave as mGluR1 agonists [7].

In this paper, we engaged ourselves in the task of thoroughly examining the conformational profile of a large series of CPGs and CPG derivatives active as mGluR ligands. The relevance of the conformational behavior in determining the observed pharmacological profile will be also discussed.

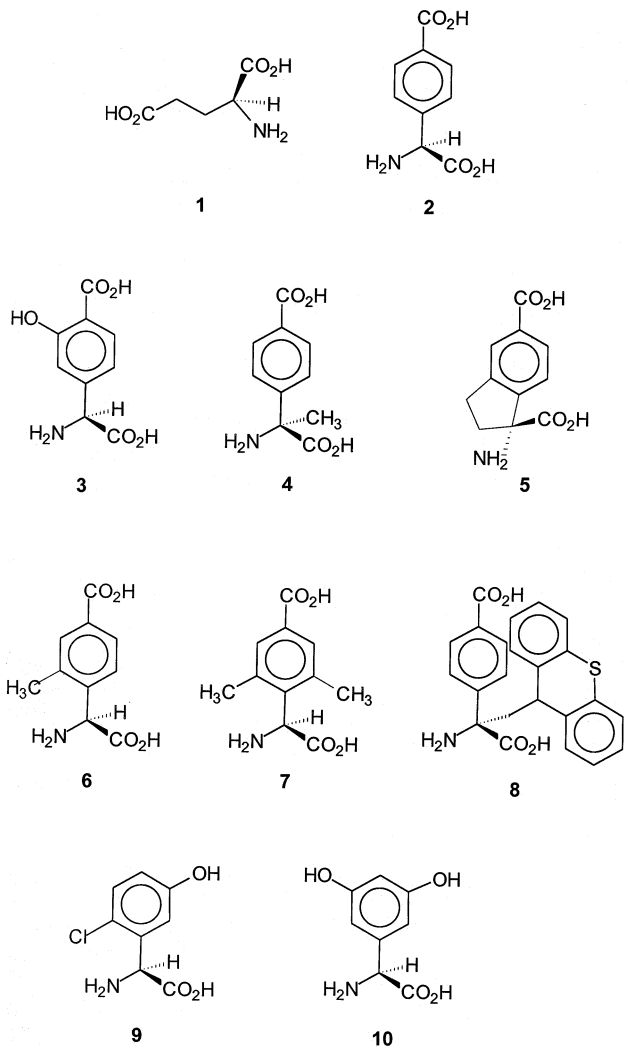


Chart 1.

2. Methods

All the compounds studied were considered in their zwitterionic form; when present, the ω-carboxylate was considered in the ionized form. Tripos force field was implemented in the program SYBYL 6.3 [8]. Calculations on highly charged molecules require the dielectric constant value to be carefully adjusted in order to correctly reproduce conformational energies and geometries. A low value of ε implies an overvaluation of the electrostatic component of the force field and, consequently, a strong and unrealistic attraction between the ω-carboxylate and the ammonium moiety. On the other hand, when the value of ε is too high, the electrostatic interactions could be neglected and the differences in energy would not be correctly reproduced. Some attempts were made by using different values for the dielectric constant and we found that the geometry was reproduced well when a distance-dependent value of $\varepsilon = 5$ was employed. Such value is not too high and, furthermore, corresponds well with the value inside a protein [9]. Gasteiger–Hückell charges were used. The Powell algorithm was used in the optimization procedure until the gradient fell below 0.05 kcal/mol Å^2. The GRID-search module of SYBYL was employed for the conformational analysis. The Boltzmann distribution was calculated with an in-house program. Moreover, where present, insight into the energy profiles of compounds were carried out using the semiempirical calculations performed by MOPAC 6.0. Where semiempirical calculations failed in giving reasonable geometries, ab initio calculations were also performed using GAUSSIAN-98 package [10].

Global minimum assignment is done on the basis of an energy criterion. However, it should be mentioned that in many cases the gap conformational energy among several encountered minimum conformations was within a range of 1 kcal/mol, which may not always be relevant in a molecular mechanics study. Nevertheless, the above criterion was used in all cases since energy differences did not affect the aim of this work.

3. Results

3.1. Conformational analysis of (S)-4-CPG (2) and (S)-4C3HPG (3)

(*S*)-4CPG (**2**) [11] is one of the first-described antagonists of mGluR1 and mGluR5, showing no activity versus ionotropic or group II and III metabotropic glutamate receptors.

The GRID-search routine was used to rotate the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle in a range from 0 to 360° using a step increment of 2°. After energy mini-

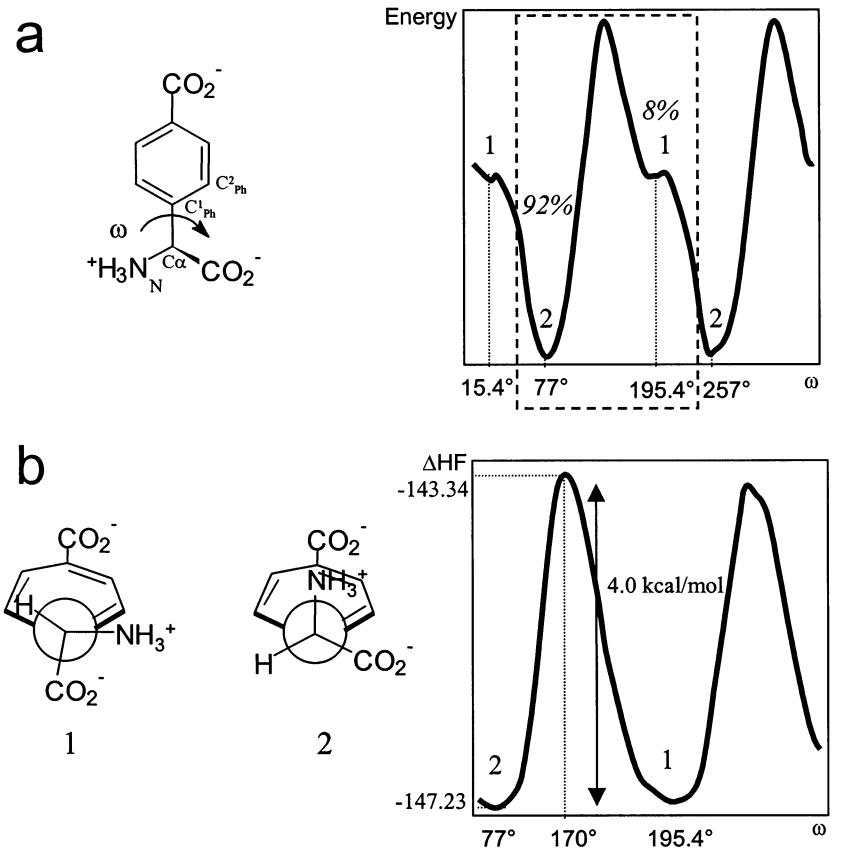


Fig. 1. (a) Conformational profile of N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle of (*S*)-4CPG (**2**); the driver search region is highlighted. (b) Minimum energy conformations and driver search plot of N–C_α–C^1_{Ph}–C^2_{Ph}.

mization of all conformers, two unique conformations were found at 15.4 and 77° with the latter being the most stable. The gap energy between both minima was calculated to be around 1.0 kcal/mol (Fig. 1).

To get more insight into the energy profile of these conformations, a driver search was carried out using MOPAC AM-1. A torsional window ranging from 50 to 230° was used with a step increment of 2°. The conformations corresponding to the maximum and minimum of energy were optimized using, respectively, the NNLSQ and AM-1 methods. The results indicate two minimum conformations in the potential surface separated by a very low energy barrier (Fig. 1).

In particular, the conformational gap energy between the saddle point and the lowest energy conformer was calculated to be around 4 kcal/mol. The Boltzmann distribution calculated at 25 °C indicates that the conformational populations for the global and local minimum conformations are of 92 and 8%, respectively. Nevertheless, since the energy barrier separating minimum conformers is low, we can argue that (*S*)-4CPG (**2**) can easily adopt any conformation between 15 and 77° with a low energy penalty.

(*S*)-4C3HPG (**3**) [12] is a moderately potent antagonist at group I mGluRs showing an agonistic profile at group II mGlu receptors and no activity versus group III mGluRs. The computational protocol used for the conformational analysis of (*S*)-4C3HPG (**3**) is the same as described for (*S*)-4CPG (**2**).

(*S*)-4C3HPG (**3**) presents four minimum conformers that can be related in pairs to those reported for (*S*)-4CPG (**2**) with the formal position of the hydroxyl group being the only difference (Fig. 2).

Fixing the formal position of the hydroxyl group in 3-position, the most stable conformer of (*S*)-4C3HPG (**3**) has the α-ammonium group almost perpendicular and below the plane defined by the aromatic ring.

3.2. Conformational analysis of (S)-MCPG (4)

(*S*)-MCPG (**4**) [4,13] is a compound having a pharmacological profile of antagonist versus group I and II and no activity at group III mGlu receptors.

The N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle was rotated in the range from 0 to 360° using a step increment of 2°.

All conformers were energetically minimized retaining the unique conformations (Fig. 3).

Thus, three minima were found at 164.0, 112.8, and 75.0° of the N–C_α–C^1_{Ph}–C^2_{Ph} torsion angle, respectively, with the latter being the most stable in energy. The

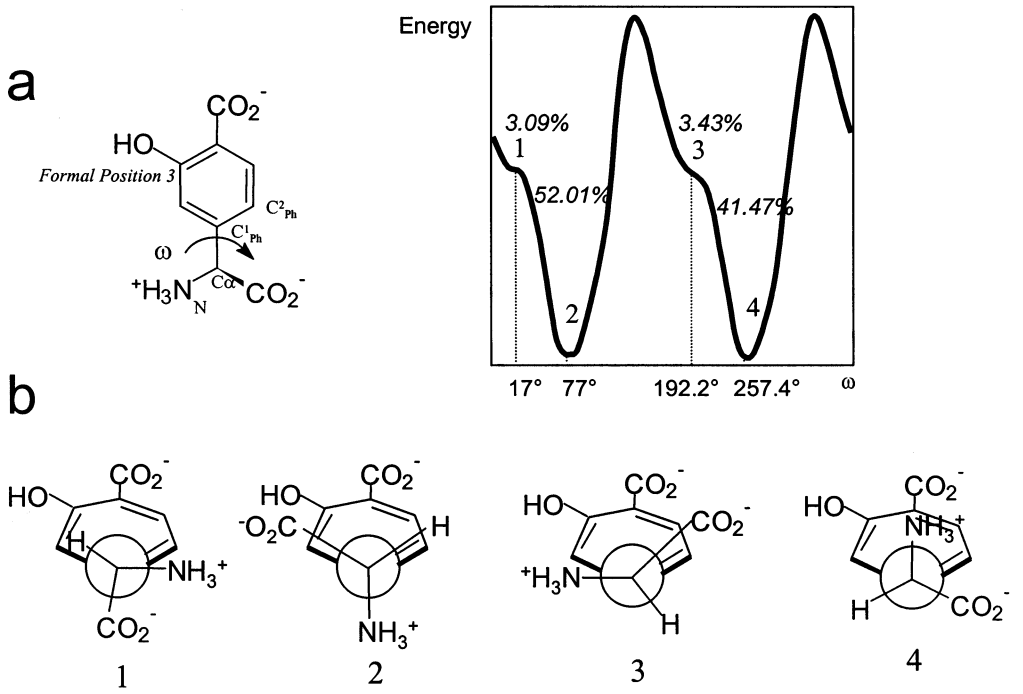


Fig. 2. (a) Conformational profile of N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle of (*S*)-4C3HPG (**3**). (b) Minimum energy conformations of (*S*)-4C3HPG (**3**).

conformational gap energy among each minimum conformation is calculated to be within 1 kcal/mol.

3.3. Conformational analysis of AIDA (5)

AIDA (**5**) [14] is a selective, although weakly potent, mGluR1 antagonist. The conformational analysis of AIDA (**5**) was performed by breaking, rotating and again bonding two torsional angles: N–C_α–C^1_{Ph}–C^2_{Ph} and C_β–C_γ–C^2_{Ph}–C^3_{Ph}. All conformations resulting from this cyclic protocol were geometrically optimized keeping only the unique ones. At the end of this process, two minimum conformations were found (Fig. 4). The most stable conformer is characterized by the position of the methylene group of the cyclopentane ring lying below the plane defined by the phenyl ring. In this conformer, the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle assumes a value of 80°. In the other minimum conformation, the methylene group is above the aromatic plane and the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle is 43°.

To gain insight into the energy profile of AIDA (**5**), semiempirical and ab initio calculations were performed on both minimum conformations.

In particular, the utilization of ab initio calculations was dictated by the computational evidence that the semiempirical protocol was unable to find a correct geometry for both minimum conformations. Indeed, a geometric optimization using the AM-1 method on AIDA (**5**) reports an unrealistic geometry where the cyclopentane moiety is placed in a flat conformation. Thus, ab initio calculations were carried out on AIDA (**5**) using a basis set of 6-31G(d) with GAUSSIAN-98 [9]. Both minimum conformations of AIDA (**5**) were correctly identified. The energy penalty between global minimum and local minimum conformations was calculated to be around 2 kcal/mol.

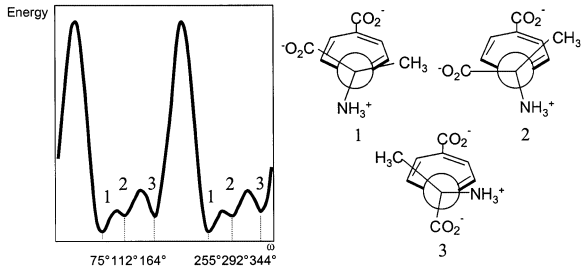


Fig. 3. Conformational profile and minimum conformations of (*S*)-MCPG (**4**).

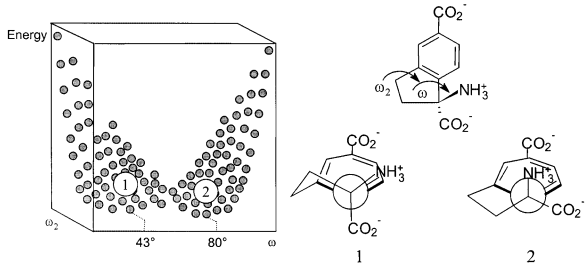


Fig. 4. Conformational profile and minimum conformations of AIDA (**5**).

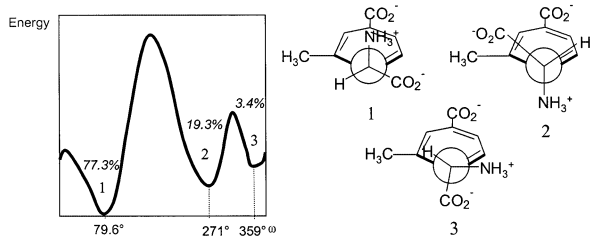


Fig. 5. Conformational profile and minimum conformations of LY-367385 (**6**).

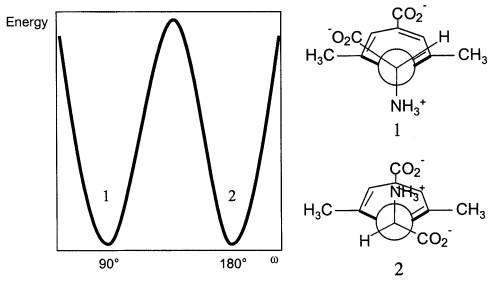


Fig. 6. Conformational profile and minimum conformations of (*S*)-4C2M6MPG (**7**).

3.4. Conformational analysis of (S)-4C2MPG (LY-367385, 6)

The 2-methyl derivative of (*S*)-4CPG (**2**) shows selectivity for mGlu1 over mGlu5 subtype receptor without activity at group II and group III receptors [5].

From a geometrical point of view, the 2-substituent breaks the symmetry of the molecule and, hence, the energetic and geometric equivalence by pairs of conformers found in (*S*)-4CPG (**2**).

A conformational search protocol similar to that described for previous compounds was adopted also in this case, with the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle being rotated in a range from 0 to 360° with a step increment of 2°.

In particular, after energy optimization of all conformations, three unique conformers were found for compound **6** (Fig. 5), with the conformer having the ammonium group situated above the phenyl ring being the most stable one.

A geometrical relationship can be found between the minimum conformations of AIDA and those of (*S*)-4C2MPG (**6**). In particular, the global minimum conformation of **6** is similar to that of AIDA unless with a lower N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle (-6.6 to 15°), while the second-encountered local minimum is analogous to the local minimum of AIDA with a higher value of the torsional angle (77–90°). The first-encountered local minimum of (*S*)-4C2MPG (**6**) does not have an equivalent in AIDA.

Since no difference is present between the conformational profiles of (*S*)-4C2MPG (**6**), AIDA (**5**) and (*S*)-4CPG (**2**), the mGluR1 selectivity of compounds **5** and **6** over mGluR5 can be explained as being a consequence of the ramification of the C^2_{Ph} atom of the benzene ring.

Moreover, the higher potency of (*S*)-4C2MPG (**6**) in relation with AIDA (**5**) could be addressed by comparing the geometrically related minimum conformations of both compounds. Indeed, these conformers show a slighter difference in the N–C_α–C^1_{Ph}–C^2_{Ph} angles moving from (*S*)-4C2MPG (**6**) to AIDA (**5**).

3.5. Conformational analysis of (S)-4C2M6MPG (7)

(*S*)-4C2M6MPG (**7**) is a derivative of the mGluR1 selective-compound (*S*)-4C2MPG (**6**) in which a second methyl moiety is introduced in the phenyl ring. This chemical modification of **6** leads to compound **7**, which has no activity at group I, II and III mGlu receptors [15].

Again, the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle was rotated in the range from 0 to 360° using a step increment of 2° and the resulting conformations were energetically minimized retaining the unique conformations. Two geometrically and energetically equivalent conformations were found as minimum points of **7** (Fig. 6). In these conformers, the ammonium group is near the normal to the plane of the aromatic ring with the value of N–C_α–C^1_{Ph}–C^2_{Ph} angle around 90°.

It is worthy to note that the rotation of the N–C_α–C^1_{Ph}–C^2_{Ph} angle is forbidden due to the steric clash between the ammonium group and methyl moieties. Indeed, when this rotation is attempted using a semiempirical AM-1 driver from 90 to 0° or from 90 to 180°, very high energy is required while the ammonium group is approaching the eclipsed conformation with one methyl group (Table 1).

3.6. Conformational analysis of LY-367366 (8)

LY367366 (**8**) is a potent antagonist of mGlu1 and mGlu5 receptors [16]. Before beginning the conformational search, a study on the possible conformations of the thioxantenyl moiety was carried out. Indeed, the saturated ring acquires a boat conformation where the methylene group can be in axial or equatorial position, with the axial being the most energetically favored conformation (data not shown). Thus, two conformational searches were performed for compound **8** considering as starting conformation, respectively, the axial and the equatorial orientation of the methylene group of the thioxantene moiety. The searches were made by rotating three torsional angles: N–C_α–C^1_{Ph}–C^2_{Ph}, N–C_α–C^1_X–C^2_X and C_α–C^1_X–C^2_X–C^3_X.

The N–C_α–C^1_{Ph}–C^2_{Ph} angle was rotated in a range of 360° using 30° of step increment; the other two angles were rotated in the same range but using 60° of step

Table 1
AM-1 driver search for the N–C_α–C^1_{Ph}–C^2_{Ph} torsional angle of compound **7**

Torsion N–C_α–C^1_{Ph}–C^2_{Ph} (°)	Heat of formation (kcal/mol)	Torsion N–C_α–C^1_{Ph}–C^2_{Ph} (°)	HF (kcal/mol)
90	−143.18	90	−143.53
95	−141.26	85	−143.43
100	−137.76	80	−141.77
105	−132.64	75	−137.83
110	−125.62	70	−131.05
115	−116.36	65	−120.47
120	−104.54	60	−104.66
125	−90.02	65	−81.71
130	−72.79	50	−49.52
135	−52.96	45	−5.96
140	−30.70	40	50.78
145	−6.14	35	121.83
150	20.76	30	207.88
155	50.30	25	310.57
160	83.12	20	433.83
165	120.27	15	582.62
170	162.67	10	760.76
175	210.98	5	997.35
180	267.24	0	1328.86

increment. A total of 637 conformations were generated. All conformations were minimized and the unique ones were kept. After this computational protocol, the number of conformations was reduced to 27 energetically and geometrically diverse conformers. The N–C_α–C^1_{Ph}–C^2_{Ph} angle presents two minima points, respectively, at 108 and 175.3° with the first one being the most energetically stable (Fig. 7).

The N–C_α–C^1_X–C^2_X and C_α–C^1_X–C^2_X–C^3_X angles adopt different minima points in an energy window of 5 kcal/mol with the most energetically stables ones being those with a π–π packing between the phenyl ring and the thioxantenyl moiety.

4. Discussion

The aim of this work is to provide conformational data for establishing the bioactive conformation of 4CPG derivatives when binding to mGluRs and to gain insight into the molecular basis of selectivity by focusing on conformational differences between active and inactive, selective and nonselective compounds.

Indeed, all 4CPGs share a unique informative torsional angle. Thus, the molecular origin of activity and selectivity of these compounds could be due to different conformations adopted by the N–C_α–C^1_{Ph}–C^2_{Ph} angle. All active derivatives of 4CPGs present at least two minima values of this torsional angle (Table 2).

The first one is characterized by the position of the ammonium group near the normal to the plane defined by the aromatic ring. In the second minimum point, the ammonium group lies on the aromatic plane. The inactive derivative of 4CPG is endowed by only one minimum conformation of N–C_α–C^1_{Ph}–C^2_{Ph} angle with the ammonium group positioned on the normal to the aromatic plane. Although a steric hindrance of the second methyl substitution of compound **7** in the binding site of the receptor cannot be ruled out (Fig. 8), the comparison of conformational profiles of 4C2M6MPG (**7**) and active 4CPGs suggests a computational evidence for the conformer with the ammonium moiety lying on the aromatic plane being the bioactive conformation.

In the same fashion, the comparison of the conformational profiles of selective (**5**, **6**) and nonselective 4CPGs allows us to gain insight into the structural basis of selectivity. Both selective (**5**, **6**) and nonselective compounds share similar minimum conformations at the N–C_α–C^1_{Ph}–C^2_{Ph} angle (Table 2). There is no computational evidence of any conformational differ-

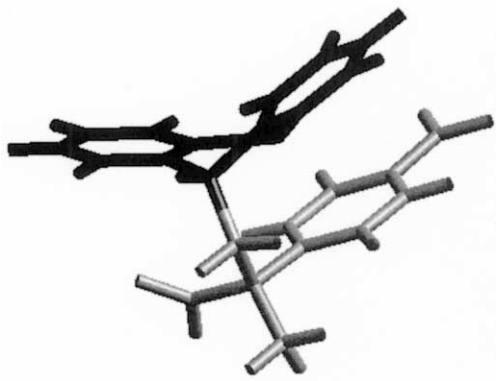
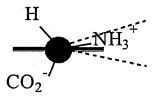
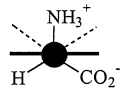


Fig. 7. Global minimum conformation of LY367366 (**8**); the thioxantenyl ring forming a π–π interaction with the phenyl ring of carboxyphenylglycine moiety is highlighted in black.

Table 2
Comparison of minimum conformations of selected CPG derivatives

Code Name	Pharmacological Profile		
		$N\text{-}C_{\alpha}\text{-}C^{1}_{Ph}\text{-}C^{2}_{Ph}$	$N\text{-}C_{\alpha}\text{-}C^{1}_{Ph}\text{-}C^{2}_{Ph}$
2	*Non-Selective*	15.4°	77.0° *
3	*Non-Selective*	17.0°	77.0° *
4	*Non-Selective*	164°	75.0° * 112.8°
5	*Selective mGluR1*	42.5°	80.0° *
6	*Selective mGluR1*	359°	79.6° * 271°
7	*Inactive*	-	90° *
8	*Non-Selective*	175.3°	108° *

Stars indicate global minimum conformations.

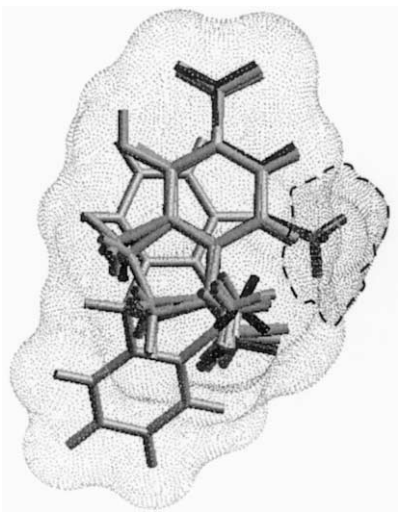


Fig. 8. Excluded volume analysis between (*S*)-4C2M6MPG (**7**) and active 4-CPG derivatives. The extra-volume of **7** is highlighted being around 10% of the sum of molecular volumes.

ence between compounds **5** and **6** and the remaining active 4CPGs. Thus, the difference in selectivity of mGlu1 subtype over mGlu5 subtype receptors of AIDA (**5**) and (*S*)-4C2MPG (**6**) should be due to different structural motifs of receptors affecting the binding mode of 4CPG-related antagonists.

In particular, the comparison of molecular volumes of selective and nonselective compounds suggests a pivotal role of a sterically forbidden region located in correspondence of the C^{2}_{Ph} position of 4CPGs in addressing mGluR1 selectivity (Fig. 9).

5. Conclusions

Conformational studies were carried out on a set of selective, nonselective and inactive 4CPG derivatives. A possible bioactive conformation of the $N\text{–}C_{\alpha}\text{–}C^{1}_{Ph}\text{–}C^{2}_{Ph}$ angle is arrived at by comparing the conformational

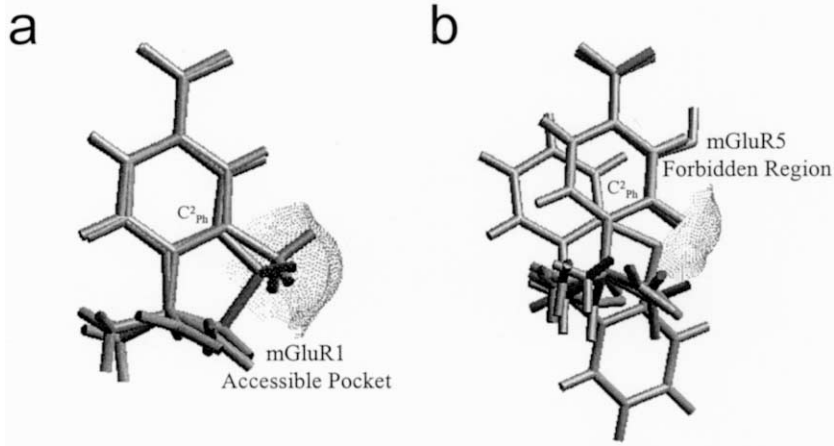


Fig. 9. Excluded volume analysis between selective and nonselective 4-CPG derivatives. mGluR1-selective compounds present an extra-volume located on C^{2}_{Ph} carbon probably corresponding to an accessible pocket in the receptor (a) which is forbidden in mGluR5 (b).

profiles of active and inactive 4CPGs. In particular, a value of that angle around 10° is needed to interact with the glutamate-binding site of mGluRs subtypes belonging to group I. This conformation is characterized by the position of the ammonium group lying on the plane defined by the aromatic ring.

No different conformational profiles exist between selective and nonselective 4CPGs. Thus, the reason why compounds **5** and **6** are selective mGluR1 antagonists should reside in different structural motifs of the binding sites of group I receptors.

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