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# Synthesis and Preliminary Biological Evaluation of 2′-Substituted 2-(3′-Carboxybicyclo[1.1.1]-pentyl)glycine Derivatives as Group I Selective Metabotropic Glutamate Receptor Ligands

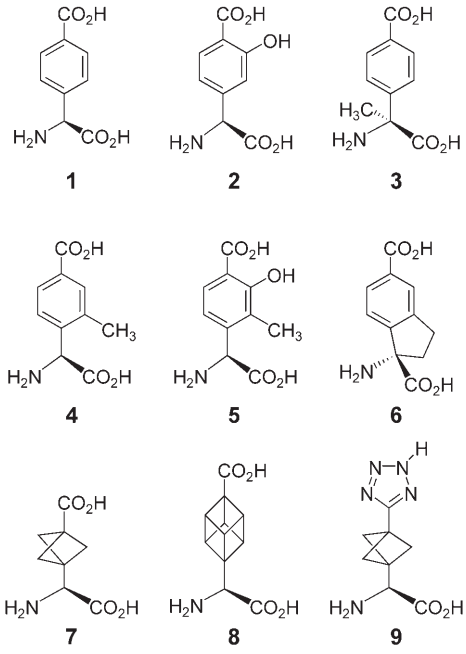
Roberto Pellicciari,*[a] Rosanna Filosa,[a] Maria Carmela Fulco,[a] Maura Marinozzi,[a] Antonio Macchiarulo,[a] Clemens Novak,[a, c] Benedetto Natalini,[a] Mette Brunsgaard Hermit,[b] Søren Nielsen,[b] Thomas Nikolaj Sager,[b] Tine Bryan Stensbøl,[b] and Christian Thomsen[b]

*The first series of 2′-substituted 2-(3′-carboxybicyclo-[1.1.1]pentyl)glycine derivatives, (2R)- and (2S)-(2′,2′-dichloro-3′-carboxybicyclo[1.1.1]pentyl)glycine (**10**) and (**11**), and 2-(2′-chloro-3′-carboxybicyclo[1.1.1]pentyl)glycine (**12**) were synthesized and evaluated as mGluR ligands. Compounds **11** and **12** were shown to be competitive group I mGluR antagonists. These results are also discussed in light of docking studies with both the active (closed) and inactive (open) conformations of mGluR1.*

## Introduction

Metabotropic glutamate receptors (mGluRs) are a family of glutamate-sensitive G-protein-coupled receptors endowed with important modulatory properties toward neuronal excitability.[1,2] Eight subtypes of these receptors, designated mGluR1 to mGluR8, have been cloned from mammalian brain tissue and classified into three groups: group I (mGluR1 and mGluR5), group II (mGluR2 and mGluR3), and group III (mGluR4, mGluR6, mGluR7, and mGluR8). This grouping is based on amino acid sequence identity, signal-transduction pathway, and pharmacological profiles.[3] The various mGluR subtypes have various functional properties, are localized heterogeneously, and represent important therapeutic targets for neurological disorders associated with increased or decreased glutamate neurotransmission. The group I subtypes (mGluR1 and mGluR5), in particular, have been the subject of intense research activity owing to their involvement in many CNS functions and their participation in a variety of disorders such as epilepsy, schizophrenia, pain, ischemia, and chronic neurodegenerative diseases.[4–7]

The great potential of group I mGluRs as therapeutic targets has accordingly elicited a great interest in the design and synthesis of group I mGluR subtype-selective competitive and noncompetitive modulators.[8] In this endeavor, members of the carboxyphenylglycine (CPG) family (compounds **1**–**5**) which were first reported by Watkins and co-workers[9] to be endowed with competitive antagonist properties against group I mGluRs, were chosen as lead compounds and subjected to a series of structural modifications aimed at improving both potency and subtype selectivity.




[a] *Prof. R. Pellicciari, Dr. R. Filosa, Dr. M. C. Fulco, Prof. M. Marinozzi, Dr. A. Macchiarulo, Dr. C. Novak, Prof. B. Natalini*
*Dipartimento di Chimica e Tecnologia del Farmaco*
*Università di Perugia, Via del Liceo, 1-06123 Perugia (Italy)*
*Fax. (+39) 075 595 5124*
*E-mail: rp@unipg.it*

[b] *Dr. M. B. Hermit, Dr. S. M. Nielsen, Dr. T. N. Sager, Dr. T. B. Stensbøl, Dr. C. Thomsen*
*H. Lundbeck A/S, 9 Ottilavej, 2500 Valby, Copenhagen (Denmark)*

[c] *Dr. C. Novak*
*On leave from Institut für Pharmazeutische Chemie*
*Universität Wien, Pharmaziezentrum, Althanstrasse 14, 1090 Wien (Austria)*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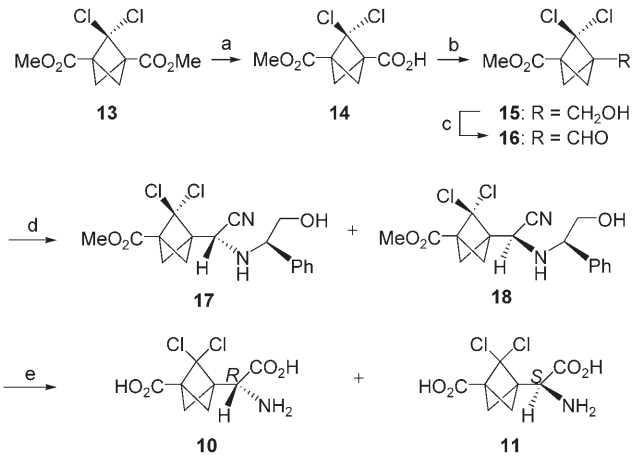
Our research group reported in 1995 that AIDA (**6**), a constrained CPG analogue, is a mGluR1 subtype-selective antagonist, and is the first to be described as capable of discriminating between the effects of the two members of the group I mGluRs.[10,11] A peculiar feature of the CPG class is the co-linearity imparted by the phenyl ring to the ω-carboxylate and the glycine moieties. With the aim of ascertaining the electronic and/or steric nature of this crucial structural feature, the aromatic ring was substituted by alicyclic spacers in a subsequent series of CPG analogues; such spacers are able to maintain the co-linearity between the two CPG pharmacophore groups.

Among them, (2*S*)-(3′-carboxybicyclo[1.1.1]pentyl)glycine ((*S*)-CBPG, **7**)[12] and (2*S*)-(3′-carboxycubyl)glycine (**8**)[13] proved to be the most interesting, and have widely been employed as pharmacological tools. The carboxybicyclo[1.1.1]pentane moiety, in particular, is a particularly interesting scaffold. Indeed, **7** showed selective mGluR1 antagonist activity ($IC_{50}$ = 25 μM), and exhibits partial agonist activity toward mGluR5 receptors.[12] This peculiar activity profile has been exploited to determine the roles that mGluR1 and mGluR5 have in CA1 pyramidal cell excitability.[14] It was also shown that **7** attenuates neuronal death in both a cortical and hippocampal model of cerebral ischemia in vitro and in vivo.[11] The interesting biological profile exhibited by (*S*)-CBPG (**7**) prompted us to further investigate its SAR profile to increase the mGluR1/mGluR5 subtype selectivity. Thus, with the goal of ascertaining the influence of the distance between the two pharmacophore groups and the role played by the distal carboxylate group, we carried out the synthesis of (2*S*)-2-(3′-(1*H*-tetrazol-5-yl)bicyclo-[1.1.1]pentyl)glycine ((*S*)-TBPG, **9**).[15] Interestingly, **9**, albeit 2.5-fold less potent as an antagonist of mGluR1 than the parent compound **7**, was found to be devoid of affinity for the mGluR5 subtype.

As a continuation of these (carboxybicyclo-[1.1.1]pentyl)glycine SAR studies, we decided to investigate how both potency and selectivity are influenced by the introduction of lipophilic moieties in the 2′-position of the core. The synthesis and preliminary biological properties of the first representatives of this new class, namely (2*R*)- and (2*S*)-(2′,2′-dichloro-3′-carboxybicyclo[1.1.1]pentyl)glycines ((*R*)-DCCBPG, **10**) and ((*S*)-DCCBPG, **11**) (Scheme 1), and 2-(2′-chloro-3′-carboxybicyclo[1.1.1]pentyl)glycine (MCCBPG, **12**) (Scheme 2), are reported herein.




**Scheme 1.** Reagents and conditions: a) 2.5 M NaOH in MeOH, THF, room temperature, 30 min, 80%; b) 1. *i*BuOCOCl, *N*-methylmorpholine, −5 °C, 30 min; 2. $NaBH_4$, $H_2O$, 0 °C, 30 min, 52%; c) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −60 °C, 2 h, 85%; d) 1. (*R*)-α-phenylglycinol, MeOH, room temperature, 24 h; 2. TMSCN, 0 °C→room temperature, 6 h, 52%; e) 1. $Pb(OAc)_4$, $CH_2Cl_2$/MeOH, 0 °C, 7 h; 2. 6 N HCl, reflux, 48 h; 3. Dowex 50WX2-200, 10% pyridine, 66%; 4. preparative CLEC. TMSCN = trimethylsilyl cyanide.

## Results and Discussion

Dimethyl 2′,2′-dichlorobicyclo[1.1.1]pentyl-1,3-dicarboxylate (**13**), obtained by chlorination and subsequent esterification of bicyclo[1.1.1]pentane-1,3-dicarboxylic acid according to the procedure developed by Michl and co-workers,[16–18] was used as the starting material for the preparation of our title compounds (Scheme 1).

Partial alkaline hydrolysis of the diester **13** provided the monoester **14**[17] (63%) that was converted into the corresponding alcohol **15** by sodium borohydride reduction of the corresponding oxyanhydride (52%). A Swern oxidation[19] of alcohol **15** led to the corresponding aldehyde **16** in 85% yield which was submitted to condensation with (*R*)-α-phenylglycinol.[20] The subsequent addition of trimethylsilyl cyanide to the Schiff base thus formed afforded a mixture of (2*R*)- and (2*S*)-α-aminonitriles **17** and **18** (52%). Contrary to expectations based on our previous experiences,[12,21] the reaction was, in this case, completely non-diastereoselective and gave a 2*S*/2*R* ratio (by HPLC) close to 1:1. The mixture of the two α-aminonitriles **17** and **18**, which could not be efficiently separated by silica gel chromatography (only a small sample of each diastereomer was obtained and used for spectroscopic characterization), was submitted to oxidative cleavage with lead tetraacetate, acidic hydrolysis, and ion-exchange chromatography to afford the corresponding amino acid (2′,2′-dichloro-3′-carboxybicyclo-[1.1.1]pentyl)glycine as a racemic mixture in 66% yield.

This racemic mixture was then submitted to HPLC preparative resolution by using a previously reported chiral-ligand-exchange methodology (CLEC),[10b] to afford (2*R*)-(2′,2′-dichloro-3′-carboxybicyclo[1.1.1]pentyl) glycine ((*R*)-DCCBPG, **10**) and (2*S*)-(2′,2′-dichloro-3′-carboxybicyclo[1.1.1]pentyl)glycine ((*S*)-DCCBPG, **11**), both in ≥99% *ee*.

The synthesis of the monochloro-substituted derivative, as outlined in Scheme 2, also started from the key intermediate dimethyl 2′,2′-dichlorobicyclo[1.1.1]pentyl-1,3-dicarboxylate (**13**).[16,17] Although the conversion of the dichloro derivative **13** into the monochloro form by the use of tributyltin hydride was previously reported (23% yield),[17] we investigated the possibility to partially reduce the dichloro function by an alternative reducing agent. In our hands, tris(trimethylsilyl)silane, reported to be an efficient substitute for tributyltin hydride in radical-based reductions,[22] was able to convert **13** into **19** in good yield (63%). Partial hydrolysis of **19** provided the monoester (±)-**20** (62%) which was converted into the corresponding alcohol (±)-**21** by sodium borohydride reduction of the

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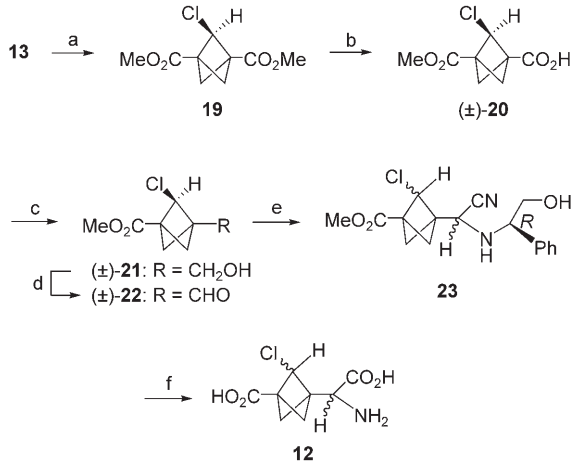


**Scheme 2.** Reagents and conditions: a) $[(CH_3)_3Si]_3SiH$, AIBN, toluene, 80 °C, 12 h, 63%; b) 2.5 M NaOH in MeOH, THF, room temperature, 30 min, 62%; c) 1. *i*BuOCOCl, *N*-methylmorpholine, −5 °C, 30 min; 2. $NaBH_4$, $H_2O$, 0 °C, 30 min, 45%; d) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, −60 °C, 2 h, 80%; e) 1. (*R*)-α-phenylglycinol, MeOH, room temperature, 24 h; 2. TMSCN, 0 °C→room temperature, 6 h, 37%; f) 1. $Pb(OAc)_4$, $CH_2Cl_2$/MeOH, 0 °C, 7 h; 2. 6 N HCl, reflux, 48 h; 3. Dowex 50WX2-200, 10% pyridine, 79%. AIBN = 2,2′-azobisisobutyronitrile.

corresponding oxyanhydride (45%). Analogously to that described above, the alcohol (±)-**21** was converted into the corresponding aldehyde (±)-**22** by Swern oxidation in 70% yield.[19] The derivative (±)-**22** was then submitted to condensation with (*R*)-α-phenylglycinol. The subsequent addition of trimethylsilyl cyanide to the Schiff base thus formed afforded the mixture of the expected four corresponding diastereomeric α-amino nitriles **23**, as two major and two minor components, endowed with (2*S*)- and (2*R*)-configuration respectively, in an approximate 3.6:1 ratio (by $^1$H NMR). As the attempts to separate the components of the mixture failed in this case as well, **23** was submitted to oxidative cleavage of the chiral auxiliary, acidic hydrolysis, and ion-exchange chromatography on Dowex 50X2-200 to afford 2-(2′-chloro-3′-carboxybicyclo-[1.1.1]pentyl)glycine (**12**) as a mixture of two pairs of enantiomers.

The new derivatives **10**, **11**, and **12** were evaluated as potential ligands of mGluRs by binding experiments. Compounds **10**, **11**, and **12** showed activity at group I mGluRs, albeit with significant diversity in potency and subtle differences in subtype selectivity (Table 1). (*S*)-DCCBPG (**11**) is the most potent compound in the series and represents the eutomer of DCCBPG at the alpha carbon. This is in agreement with the stereochemical preference of (*S*)-glutamate that binds mGluRs. Interestingly, MCCBPG (**12**) is endowed with a slightly higher mGluR1/mGluR5 selectivity index than those of **10** and **11**. When tested in functional assays to measure glutamate-induced increases in inositol phosphates,[10] **10**, **11**, and **12** were antagonists at both mGluR1 and mGluR5 (data not shown). All compounds were inactive at prototypic group II and group III mGluR subtypes (mGluR2 and mGluR4, $K_i > 1000$ μM). When tested in vivo in mice, **11** was effective at inhibiting NMDA-induced convulsions after intracerebroventricular (icv) injection (Figure 1).

**Table 1.** Biological data of tested compounds at mGluR1 and mGluR5.

| Compd | mGluR1 $K_i$ [μM][a] | mGluR5 $K_i$ [μM][a] | Selectivity Index [mGlu1/mGlu5] |
|---|---|---|---|
| (*S*)-DCCBPG (**11**) | 3 | 13 | 0.23 |
| (*R*)-DCCBPG (**10**) | 25 | 62 | 0.40 |
| MCCBPG (**12**) | 19 | 125 | 0.15 |
| (*S*)-CBPG (**7**) | 25[b] | 103[c] | – |

[a] [$^3$H]Quisqualate binding experiments were performed on rmGluR1 and rmGluR5 receptor-expressing cell membranes as described previously.[10] Data represent the mean of at least three independent experiments performed in triplicate. [b] $IC_{50}$ [μM] from Ref. [12]. [c] $EC_{50}$ [μM] from Ref. [12].

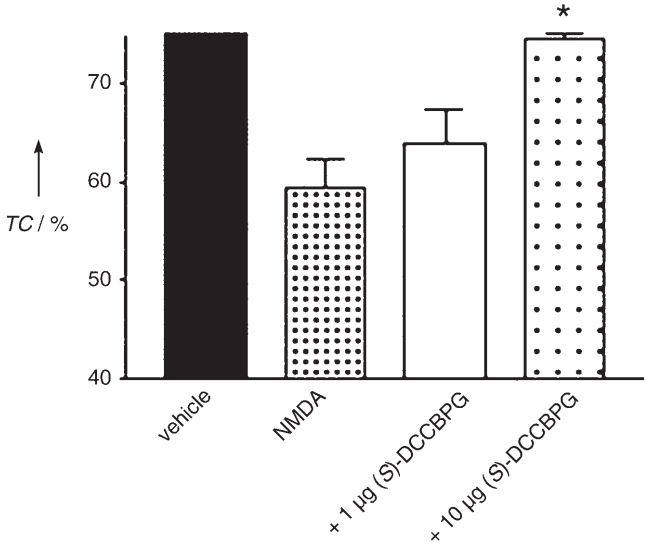


**Figure 1.** In vivo anticonvulsant activity of (*S*)-DCCBPG (**11**). Thresholds to convulsions (*TC*) in mice were measured after icv infusion of *N*-methyl-D-aspartate (NMDA). NMDA was co-infused with either vehicle or the test compound as indicated. *: $p < 0.05$ relative to NMDA alone. (*S*)-DCCBPG (**11**) did not affect basal locomotor activity and did not induce convulsions when injected alone. MK-801 (0.3 mg kg$^{-1}$, subcutaneous) completely protected against NMDA-induced seizures.

To shed light on the binding mode and to explain the pharmacological profile of compounds **11** and **12**, docking experiments were performed with AutoDock v3.0[23] in both the open (functionally inactive) and closed (active) conformations of mGluR1 (each conformation was retrieved from a single dimeric crystal structure; PDB code: 1ewk). Docking experiments were also performed on compound **7**. The reason for carrying out experiments on both conformations of the receptor was to adopt a blind condition regarding the pharmacological profile of the above compounds. In this situation, we analyze the molecular basis of the antagonism of compounds **7**, **11**, and **12** by comparing results obtained in both the active and inactive conformations of mGluR1. This is, in fact, the common blind situation during structure-based design and structure-based

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virtual screening in which we lack any information about functional data. Results obtained in this way may therefore give hints regarding the appropriate scoring scheme to adopt for cases in which compounds endowed with antagonistic properties are studied. The following stereoisomers (*S*)-CBPG (**7**), (*S*)-DCCBPG (**11**), (2*S*,2′*R*)-MCCBPG, and (2*S*,2′*S*)-MCCBPG were considered for docking experiments. For each docking pose, the root mean square deviation (RMSD) from the experimental bioactive conformation of (*S*)-glutamate in the closed and open state of the receptor was calculated by using the atomic coordinates of the respective amino acid moieties and distal carboxylic groups. Results were clustered and ranked by ascending RMSD and binding energy ($E_b$) values. Only the best-ranked solutions are shown in Table 2.

**Table 2.** RMSD and binding energies of best-docked solutions.

| Compd | Closed Conformation | | Open Conformation | |
|---|---|---|---|---|
| | RMSD [Å] | $E_b$ [kcal mol$^{-1}$] | RMSD [Å] | $E_b$ [kcal mol$^{-1}$] |
| (*S*)-DCCBPG (**11**) | 3.01 | −11.4 | 2.43 | −8.68 |
| (2*S*,2′*R*)-MCCBPG | 1.82 | −11.6 | 2.97 | −7.38 |
| (2*S*,2′*S*)-MCCBPG | 2.38 | −11.8 | 2.36 | −7.24 |
| (*S*)-CBPG (**7**) | 2.27 | −11.7 | 2.78 | −8.19 |

All compounds yielded similar binding energies when docked at the closed active conformation of mGluR1. (2*S*,2′*R*)-MCCBPG showed the lowest RMSD (1.82 Å) from the bioactive conformation of glutamate (Figure 2). This value is not low enough to determine an agonistic profile for (2*S*,2′*R*)-MCCBPG. Functional data, indeed, pinpoints an antagonistic activity toward mGluR1 for compound **12**. However, it should be mentioned that in this case, any structure–activity relationship suffers from the fact that **12** has been tested as a racemic mixture and its functional data reflects the action of its four stereoisomers.

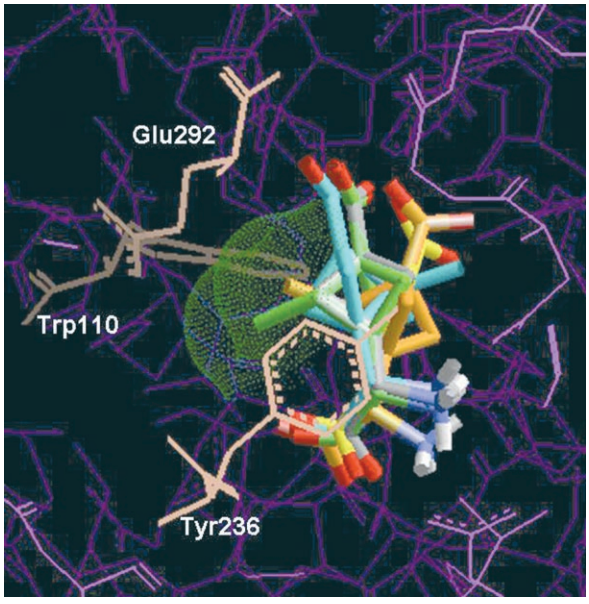


**Figure 2.** Best-docked solutions of (*S*)-DCCBPG (**7**, gray), (*S*)-DCCBPG (**11**, cyan), (2*S*,2′*R*)-MCCPBG (orange) and (2*S*,2′*S*)-MCCBPG (green) into the closed conformation of mGluR1. The bioactive conformation of (*S*)-glutamate is also shown (yellow). The green dots highlight the narrow binding pocket.

In the docked pose, chlorine atoms adopt different positions in the diastereomeric pair (2*S*,2′*R*)- and (2*S*,2′*S*)-MCCBPG, and (*S*)-DCCBPG (**11**). In (2*S*,2′*R*)- and (2*S*,2′*S*)-MCCBPG, the chlorine atom rests in a narrow binding pocket composed of Trp 110, Tyr 236, and Glu 292, where it adopts an *anti* conformation with respect to the amino group (Figure 3). The insertion of

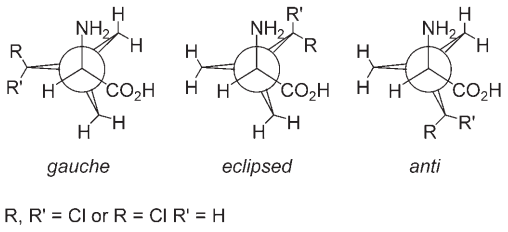


**Figure 3.** Different bioactive conformations adopted by (*S*)-DCCBPG (**11**), (2*S*,2′*R*)-MCCPBG and (2*S*,2′*S*)-MCCBPG.

two chlorine atoms at the 2′-position is too sterically demanding to fit the above pocket, and therefore (*S*)-DCCBPG (**11**) is forced to adopt an *eclipsed* conformation (Figure 3). Notably, the differing fit of the chlorine atoms into the narrow binding pocket explains the diverse RMSD values of compounds as reported in Table 2.

The results of docking experiments into the open conformation of mGluR1 reveal a slight increase in binding energy for (*S*)-CBPG (**7**) and (*S*)-DCCBPG (**11**) over that of (2*S*,2′*R*)- and (2*S*,2′*S*)-MCCBPG. All compounds have similar RMSD values calculated on the pharmacophore points of (*S*)-glutamate. (*S*)-DCCBPG (**11**), (2*S*,2′*R*)-, and (2*S*,2′*S*)-MCCBPG share a common bioactive conformation in which the chlorine atoms adopt a *gauche* positioning with respect to the amino group (Figure 3). In the docked pose, the chlorine atoms are positioned toward the upper lobe (Figure 4).

The comparison of binding energies in the closed and open states of the receptor indicates that those at the closed active conformation are slightly lower than the binding energies at the open conformation of mGluR1. Thus, it is not possible to explain the pharmacological profile of compounds **7**, **11**, and **12** relying purely on a scoring scheme based on binding energies. Indeed, antagonists are expected to bind with higher affinity at the inactive conformation of the receptor. The disagreement between binding energies and the observed pharmacological profile is overcome by the inspection of RMSD values from the bioactive conformation of (*S*)-glutamate.

The high RMSD values of compounds **7**, **11**, and **12** indicate that disfavored van der Waals interactions between these ligands and the binding site hamper the compounds from adopting the docking pose of (*S*)-glutamate both in the open and closed states of the receptor. This docking pose represents the appropriate fitting of the binding site required to trigger the activation of the receptor though its closure. Thus, an ago-

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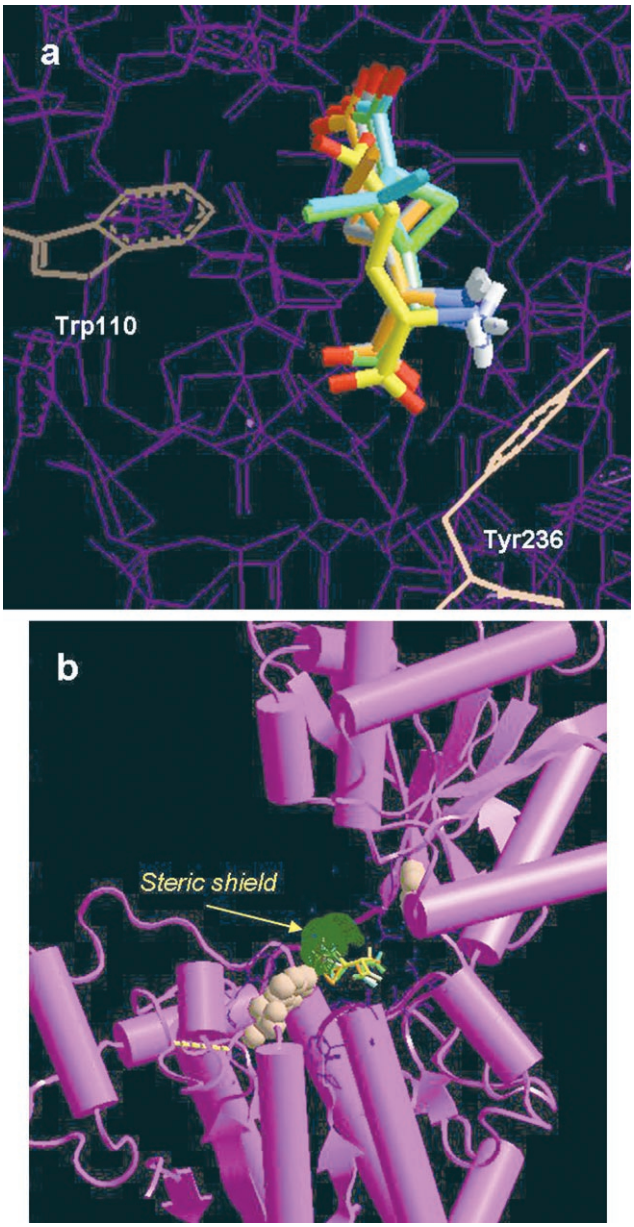


**Figure 4.** a) Best-docked solutions of (*S*)-DCCBPG (**7**, gray), (*S*)-DCCBPG (**11**, cyan), (2*S*,2′*R*)-MCCPBG (orange) and (2*S*,2′*S*)-MCCBPG (green) into the open conformation of mGluR1; the bioactive conformation of (*S*)-glutamate is also shown (yellow). b) The green dots highlight the positions of chlorine atoms.

nist is expected to fit the interaction points of (*S*)-glutamate as observed in the crystal structure of the receptor, whereas an antagonist does not. Following this consideration, all compounds would be antagonists of mGluR1 providing disfavored van der Waals interactions to receptor closure through a different pose from (*S*)-glutamate. This is also evidenced by the bioactive *gauche* conformation of compounds **11** and **12** in the open state of mGluR1 which do not fit the closed state, in which these compounds are forced to adopt different conformations.

As the closure of the binding site is the initial conformational change that leads to receptor activation, the overall effect of these compounds would be to stabilize the resting, open conformation of mGluR1. Notably, compound **7** is an antagonist of mGluR1 but a partial agonist of mGluR5, although it lacks 2′-substitution. Compounds **11** and **12** are antagonists of both mGlu1 and mGlu5 receptors.

Although docking experiments were not carried out on mGluR5 for which there is no crystal structure available, we can propose that the position of chlorine atoms toward the upper lobe (Figure 4) would impede the closure of both mGlu1 and mGlu5 receptors through the formation of an additional shield of steric hindrance. (*S*)-CBPG (**7**), which lacks 2′-substitution, is still able to block the closure of mGluR1 through disfavored van der Waals interactions as discussed above, but the absence of the steric shield is sufficient to allow a partial activation of mGluR5. It is clear that further docking experiments on mGluR5 will help to clarify this point when the crystal structure of this receptor is available.

## Conclusion

Two new competitive mGluR modulators that belong to the novel class of 2′-substituted (3′-carboxybicyclo-[1.1.1]pentyl)glycines have been presented. These compounds have been shown to have binding properties at group I receptor subtypes. Functional assays point out that compounds **11** and **12** antagonize glutamate-induced responses in both mGlu1 and mGlu5 receptors.

In particular, compound **11** is effective at inhibiting NMDA-induced convulsions in vivo when injected intracerebroventricularly in mice. Docking studies carried out both in the closed functionally active and open conformations of mGluR1 aid in ascribing the antagonistic pharmacological profile of compounds **7**, **11**, and **12** to the presence of disfavored van der Waals interactions. These disfavored interactions arise from a different pose assumed by these compounds with respect to (*S*)-glutamate and hamper the closure of the receptor and, in turn, its activation. The position of chlorine atoms of 2′-substituted derivatives **11** and **12** in the binding site of the open state of mGluR1 allows us to infer a possible explanation for the loss of partial agonism of these compounds at mGluR5 relative to (*S*)-CBPG (**7**). Indeed, chlorine atoms enforce the presence of disfavored van der Waals interactions to receptor closure through additional steric hindrance. These added hindrances are required to warrant the antagonism at mGluR5. The reported compounds represent potential leads for group I mGluR competitive antagonists and useful pharmacological tools for use in further characterizations of this receptor subtype.

## Experimental Section

All reagents were analytical-grade and purchased from Sigma–Aldrich (Milan, Italy). Flash chromatography was performed on Merck silica gel (0.040–0.063 mm). Melting points were determined in open capillary tubes on a Büchi 535 electrothermal apparatus and are uncorrected. $^{1}$H NMR and $^{13}$C NMR spectra were registered on a Bruker AC 200 or Bruker AC 400 with $CDCl_3$ as solvent, unless otherwise indicated. Chemical shifts are reported in ppm. The abbrevi-

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ations used are as follows: s, singlet; d, doublet; dd, double doublet; bs, broad signal. Optical rotations were recorded on a Jasco Dip-360 digital polarimeter. The analytical HPLC analyses were carried out on a Shimadzu (Kyoto, Japan) Workstation Class LC-10 equipped with a CBM-10 A system controller, two LC-10 AD high-pressure binary gradient delivery systems, an SPD-10 A variable wavelength UV/Vis detector, and a Rheodyne 7725i injector (Rheodyne Inc., Cotati, CA, USA) with a stainless steel loop (vol = 20 μL). The analytical mobile phase was prepared by dissolving copper(II) acetate (1.0 mM) and *N*,*N*-$Me_2$-*S*-Phe (2.0 mM) separately in HPLC-grade water; the latter solution was adjusted to pH ≈4.0 with AcOH. The solutions were then mixed, filtered through a Millipore filter (0.45 μM, Bedford, MA), degassed by sonication (10 min), and the pH was readjusted. A LiChrospher 100 RP-18 analytical column (Merck–VWR, 250×4.0 mm i.d., 5 μM, 100 Å) was conditioned by recycling the selected mobile phase for at least 24 h. For the analytical tests, analytes were prepared in approximate concentrations of 0.1–0.5 mg $mL^{-1}$ in filtered mobile-phase components and sonicated until completely dissolved. UV/Vis detection was performed at $\lambda = 254$ and 210 nm, and the flow rate was 1.0 mL $min^{-1}$. Injection of $NaNO_2$ was performed for the calculation of all chromatographic parameters. The chiral mobile phase used for the preparative separations was composed of buffered (pH 4.0) $Cu^{II}$ acetate (0.5 mM) and *N*,*N*-$Me_2$-*S*-Phe (1.0 mM). The flow rate was 13.0 mL $min^{-1}$, and UV/Vis detection was set at $\lambda = 254$ nm. A LiChrospher 100 RP-18 semipreparative column (Merck–VWR, 250× 25 mm i.d., 5 μm, 100 Å) was conditioned by recycling the selected mobile phase for at least 30 h. The preparative HPLC system consisted of a Shimadzu LC-8 A pump, an SPD-10 Avp variable wavelength UV/Vis detector, and a Rheodyne 7725i injector with a stainless steel loop (vol = 2 mL). The chromatographic profile was obtained with CLASS VP (Shimadzu, v4.3) software. Cation- and anion-exchange chromatography were performed with Dowex 50WX2–200 and Dowex 1X8–200, respectively.

**2,2-Dichloro-3-(methoxycarbonyl)bicyclo[1.1.1]pentane-1-carboxylic acid (14)**: A solution of NaOH in methanol (2.5 M, 2.95 mL) was added dropwise to a magnetically stirred solution of dimethyl 2′,2′-dichlorobicyclo[1.1.1]pentyl-1,3-dicarboxylate (**13**)[16,17] (0.190 g, 7.38 mmol) in dry THF (57 mL), and the resulting mixture was stirred at room temperature for 30 min. The solvent was partially removed, the residue was diluted with water (50 mL), and the aqueous phase was extracted with $CH_2Cl_2$ (3×30 mL). Evaporation of the combined organic extracts gave the residual starting material **13** (0.430 g, 23%). The aqueous layer was acidified to pH 3 with 12 N HCl and extracted with $CH_2Cl_2$ (3×30 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated to afford **14** (0.112 g, 80%) as a pale-yellow solid; $^1$H NMR (200 MHz): $\delta = 2.56$ (s, 2H, $CH_2$), 3.10 (s, 2H, $CH_2$), 3.85 (s, 3H, $CO_2CH_3$), 9.8 ppm (bs, 1H, COOH); $^{13}$C NMR ($CDCl_3$): $\delta =$ 49.73, 52.62, 91.13, 164.92, 169.91 ppm.

**Methyl 2,2-dichloro-3-(hydroxymethyl)bicyclo[1.1.1]pentane-1-carboxylate (15)**: Isobutyl chloroformate (0.703 g, 5.15 mmol) was added dropwise to a cold (−5 °C) solution of **14** (0.103 g, 4.29 mmol) and 4-methylmorpholine (0.521 g, 5.15 mmol) in dry THF (7 mL). The reaction mixture was magnetically stirred at −5 °C under an argon atmosphere for 30 min and then filtered. The solution was added dropwise to a cold (0 °C) stirred solution of $NaBH_4$ (0.320 g, 8.58 mmol) in $H_2O$ (27 mL). The cooling bath was removed, and stirring was continued at room temperature for 30 min, after which the reaction mixture was neutralized with 2 N HCl, and the organic solvent evaporated off. The aqueous phase was extracted with AcOEt (3×10 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered, and evaporated to give a residue that was submitted to flash chromatography. Elution with light petroleum/AcOEt (1:1) afforded **15** (0.108 g, 52%) as a pale-yellow oil; $^1$H NMR (200 MHz): $\delta = 1.76$ (bs, 1H, $CH_2OH$), 2.13 (s, 2H, $CH_2$), 2.67 (s, 2H, $CH_2$), 3.72 (s, 3H, $CO_2CH_3$), 3.82 ppm (s, 2H, $CH_2OH$); $^{13}$C NMR (50 MHz): $\delta = 47.28$, 52.33, 53.40, 55.92, 57.76, 91.60, 165.64 ppm.

**Methyl 2,2-dichloro-3-formylbicyclo[1.1.1]pentane-1-carboxylate (16)**: A solution of DMSO (0.436 g, 5.59 mmol) in dry $CH_2Cl_2$ (1.5 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (0.355 g, 2.80 mmol) in dry $CH_2Cl_2$ (5.0 mL) kept at −60 °C under an argon atmosphere. After 5 min, a cooled (−78 °C) solution of the alcohol **15** (0.570 g, 2.54 mmol) in dry $CH_2Cl_2$ (3.0 mL) was added dropwise over the course of 5 min. The reaction mixture was stirred at −60 °C for 2 h. Triethylamine (1.28 g, 12.71 mmol) was then added dropwise over 5 min, and the stirred solution was allowed to warm to room temperature. Water (12 mL) was then added, the organic layer separated, and the aqueous phase extracted with $CH_2Cl_2$ (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated to give a residue that was submitted to flash chromatography. Elution with light petroleum/AcOEt (3:2) afforded **16** (0.760 g, 85%) as a pale-yellow oil; $^1$H NMR (200 MHz): $\delta = 2.51$ (s, 2H, $CH_2$), 3.09 (s, 2H, $CH_2$), 3.84 (s, 3H, $CO_2CH_3$), 9.78 ppm (s, 1H, CHO); $^{13}$C NMR (50 MHz): $\delta = 46.15$, 49.06, 52.56, 57.57, 90.50, 165.90, 193.07 ppm.

**(2*S*)- and (2*R*)-*N*-[(*R*)-α-Phenylglycinyl]-2-[2′,2′-dichloro-3′-methoxycarbonyl-1-bicyclo[1.1.1] pentane]glycinonitriles (17+18)**: (*R*)-α-Phenylglycinol (0.110 g, 0.79 mmol) was added to a solution of **16** (0.180 g, 0.79 mmol) in dry MeOH (10 mL), and the resulting solution was magnetically stirred at room temperature for 2 h under an argon atmosphere. After cooling to 0 °C, TMSCN (0.157 g, 1.59 mmol) was added, and the resulting mixture was stirred for 12 h at room temperature. Evaporation of the solvent gave a residue that was submitted to flash chromatography. Elution with light petroleum/AcOEt (4:1) afforded the inseparable mixture of (**17**+**18**) (0.150 g, 52%); **17**: $^1$H NMR (400 MHz): $\delta = 2.27$ (d, $J =$ 3.1 Hz, 1H, 4′-$CH_a$), 2.33 (d, $J = 3.1$ Hz, 1H, 5′-$CH_a$), 2.80 (dd, $J = 3.1$ and 10.9 Hz, 1H, 4′-$CH_a$), 2.89 (dd, $J = 3.1$ and 10.9 Hz, 1H, 5′-$CH_a$), 3.96 (dd, $J = 7.9$ and 11.0 Hz, 1H, $CH_aOH$), 3.80–3.84 (m, 3H, $CO_2CH_3$ and $CH_bOH$), 4.06 (dd, $J = 4.1$ and 7.7 Hz, 1H, *CH*Ph), 4.17 (s, 1H, CHCN), 7.31–7.42 (m, 5H, aromatics); $^{13}$C NMR (100 MHz): $\delta = 46.47$, 47.59, 48.17, 52.91, 53.18, 54.70, 63.89, 67.08, 91.39, 117.03, 127.84, 128.99, 129.41, 139.18, 165.11. **18**: $^1$H NMR (400 MHz): $\delta = 2.34$ (d, $J = 3.1$ Hz, 1H, 4′-$CH_a$), 2.38 (d, $J = 3.1$ Hz, 1H, 5′-$CH_a$), 2.80 (dd, $J =$ 3.1 and 10.9 Hz, 1H, 4′-$CH_a$), 2.91 (dd, $J = 3.1$ and 10.9 Hz, 1H, 5′-$CH_a$), 3.56–3.84 (m, 6H, $CH_2OH$, $CO_2CH_3$ and CHCN), 4.12 (dd, $J = 4.1$ and 7.8 Hz, *CH*Ph), 7.38–7.42 ppm (m, 5H, aromatics); $^{13}$C NMR (100 MHz): $\delta = 45.09$, 47.23, 47.65, 52.54, 54.04, 62.92, 67.31, 90.14, 116.61, 127.67, 128.60, 129.07, 138.80, 164.72 ppm.

**(2*R*)- and (2*S*)-2-(2′,2′-Dichloro-3′-carboxybicyclo[1.1.1]pentyl)-glycine (10) and (11)**: Lead(IV) acetate (0.260 g, 0.58 mmol) was added to a cold (0 °C) magnetically stirred solution of (**17**+**18**) (0.180 g, 0.480 mmol) in dry $CH_2Cl_2$/MeOH (12 mL, 2:1). After 10 min, the cooling bath was removed, and stirring continued for 20 min. Water (12 mL) was then added, and the resulting mixture was filtered with the aid of celite. The organic phase was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×10 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated off to afford a residue (0.180 g) that was heated at reflux in 6 N HCl (15 mL) for 24 h. After cooling, the reaction mixture was washed with $CH_2Cl_2$ (2×5 mL)

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and evaporated to dryness. The residue (0.140 g) was submitted to ion-exchange chromatography on Dowex 50WX2-200. Elution with 5% pyridine afforded the racemic mixture (0.081 g, 66%) as a pale-yellow solid; $^1$H NMR ($D_2O$, 400 MHz): $\delta = 2.02$ (d, $J = 5.3$ Hz, 2H, $CH_2$), 2.54 (s, 2H, $CH_2$), 3.86 ppm (s, 1H, 2-CH); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta = 47.71$, 48.43, 51.76, 52.83, 54.33, 91.72, 170.06, 171.15 ppm. Repeated injections (3–4 mg) of this racemate (0.061 g) in the semipreparative column allowed the baseline separation of two peaks composed of the two diastereomeric complexes ($k'_R$ 5.27, $k'_S$ 10.64, $\alpha$ 2.02, R 5.27), which were collected and carefully evaporated to dryness. After tandem cation/anion-exchange chromatography,[10b] (2*S*)-2-(2′,2′-dichloro-3′-carboxybicyclo-[1.1.1] pentyl)glycine (**10**, 0.015 g) and (2*S*)-2-(2′,2′-dichloro-3′-carboxybicyclo[1.1.1] pentyl)glycine (**11**, 0.013 g) were obtained. Subsequent HPLC analysis confirmed a purity of $\geq$99% and $\geq$99% *ee* for both enantiomers.

**Dimethyl 2-chlorobicyclo[1.1.1]pentane-1,3-dicarboxylate (19)**: A solution of **13** (1.250 g, 4.05 mmol), tris(trimethylsilyl)silane (1.210 g, 4.86 mmol), and AIBN (0.154 g, 0.94 mmol) in dry toluene (315 mL) was heated at 80 °C for 12 h. Evaporation of the solvent gave a residue which was purified by flash chromatography. Elution with hexane/AcOEt (9:1) provided **19** (0.560 g, 63%); $^1$H NMR (200 MHz): $\delta = 2.16$ (dd, $J = 3.0$ and 10.0 Hz, 1H, 4-$CH_a$), 2.30 (dd, $J = 3.0$ and 7.0 Hz, 1H, 5-$CH_a$), 2.50 (d, $J = 3.0$ Hz, 1H, 5-$CH_b$), 3.10 (dd, $J = 3.0$ and 7.0 Hz, 1H, 4-$CH_a$), 3.55 (s, 6H, 2×$CO_2CH_3$), 4.5 ppm (d, $J = 7.0$ Hz, 1H, CHCl); $^{13}$C NMR (50 MHz): $\delta = 43.86$, 48.04, 48.61, 52.10, 70.32, 166.80 ppm.

**(±)-2-Chloro-3-methoxycarbonylbicyclo[1.1.1]pentane-1-carboxylic acid (20)**: A solution of NaOH in methanol (2.5 M, 1.27 mL) was added dropwise to a magnetically stirred solution of **19** (0.695 g, 3.18 mmol) in dry THF (22 mL), and the resulting mixture was stirred at room temperature for 30 min. The solvent was partially removed in vacuo, the residue was diluted with water (50 mL), and the aqueous phase extracted with $CH_2Cl_2$ (3×25 mL). Evaporation of the combined organic extracts gave the residual starting material **19** (0.063 g, 9%). The aqueous layer was acidified to pH 3 with 12 N HCl and extracted with $CH_2Cl_2$ (3×25 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated to afford **20** (0.400 g, 62%) as a pale-yellow solid; mp: 83–86 °C; $^1$H NMR (200 MHz): $\delta = 2.16$ (dd, $J = 3.0$ and 10.0 Hz, 1H, 4-$CH_a$), 2.30 (dd, $J = 3.0$ and 7.0 Hz, 1H, 5-$CH_a$), 2.50 (d, $J = 3.0$ Hz, 1H, 5-$CH_b$), 3.10 (dd, $J = 3.0$ and 7.0 Hz, 1H, 4-$CH_b$), 3.55 (s, 3H, $CO_2CH_3$), 4.50 (d, $J = 7.0$ Hz, 1H, CHCl), 10.89 ppm (bs, 1H, COOH); $^{13}$C NMR (50 MHz): $\delta = 43.73$, 43.86, 48.04, 48.72, 52.29, 70.20, 166.80, 172.09 ppm.

**(±)-Methyl 2-chloro-3-hydroxymethylbicyclo[1.1.1]pentane-1-carboxylate (21)**: Isobutyl chloroformate (0.558 g, 4.23 mmol) was added to a cold (−5 °C) solution of **20** (0.550 g, 2.69 mmol) and 4-methylmorpholine (0.407 g, 4.23 mmol) in dry THF (2.5 mL). The reaction mixture was magnetically stirred at −5 °C under an argon atmosphere for 30 min and then filtered. The solution was added dropwise to a cold (0 °C) stirred solution of $NaBH_4$ (0.204 g, 5.38 mmol) in $H_2O$ (15 mL). The cooling bath was removed, and stirring was continued at room temperature for 30 min after which the reaction mixture was neutralized with 2 N HCl and the organic solvent evaporated off. The aqueous phase was extracted with AcOEt (3×10 mL), and the combined organic phases were dried over $Na_2SO_4$, filtered, and evaporated to give a residue that was submitted to flash chromatography. Elution with light petroleum/AcOEt (7:3) afforded **21** (0.230 g, 45%) as a pale-yellow oil; $^1$H NMR: $\delta = 1.95$ (dd, $J = 3.0$ and 10.0 Hz, 1H, 5-$CH_a$), 2.10 (dd, $J = 3.0$ and 7.0 Hz, 1H, 4-$CH_a$), 2.25 (d, $J = 3.0$ Hz, 1H, 4-$CH_b$), 2.75 (dd, $J = 3.0$ and 7.0 Hz, 1H, 5-$CH_b$), 3.5 (d, $J = 4.7$ Hz, 2H, C$H_2$OH), 3.65 (s, 3H, $CO_2CH_3$), 4.5 ppm (d, $J = 7.0$ Hz, 1H, CHCl); $^{13}$C NMR (50 MHz): $\delta = 44.53$, 45.73, 45.96, 46.54, 52.00, 58.96, 69.07, 167.68 ppm.

**(±)-Methyl 2-chloro-3-formylbicyclo[1.1.1]pentane-1-carboxylate (22)**: A solution of DMSO (0.362 g, 4.64 mmol) in dry $CH_2Cl_2$ (1.0 mL) was added dropwise to a magnetically stirred solution of oxalyl chloride (0.294 g, 2.32 mmol) in dry $CH_2Cl_2$ (5.0 mL) kept at −60 °C under an argon atmosphere. After 5 min, a cooled (−78 °C) solution of **21** (0.400 g, 2.11 mmol) in dry $CH_2Cl_2$ (2.0 mL) was added dropwise over the course of 5 min. The reaction mixture was stirred at −60 °C for 2 h. Triethylamine (0.864 g, 8.55 mmol) was then added dropwise over 5 min, and the stirred solution was allowed to warm to room temperature. Water (12 mL) was then added, the organic layer separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated to give a residue that was submitted to flash chromatography. Elution with light petroleum/AcOEt (3:2) afforded **22** (0.320 g, 80%), which was used immediately for the next step; $^1$H NMR (200 MHz): $\delta = 2.16$ (dd, $J = 3.0$ and 10.0 Hz, 1H, 4-$CH_a$), 2.30 (dd, $J = 3.0$ and 7.0 Hz, 1H, 4-$CH_b$), 2.50 (d, $J = 3.0$ Hz, 1H, 5-$CH_b$), 3.10 (dd, $J = 3.0$ and 7.0 Hz, 1H, 4-$CH_b$), 3.55 (s, 3H, $CO_2CH_3$), 4.5 (d, $J = 7.0$ Hz, 1H, CHCl), 9.50 ppm (s, 1H, CHO).

***N*-[(*R*)-α-Phenylglycinyl]-2-[2′-chloro-3′-methoxycarbonyl-1-bicyclo[1.1.1]pentane]glycinonitriles (23)**: (*R*)-α-Phenylglycinol (0.233 g, 1.70 mmol) was added to a solution of **22** (0.320 g, 1.70 mmol) in dry MeOH (17 mL), and the resulting solution was magnetically stirred at room temperature for 1.5 h under an argon atmosphere. After cooling to 0 °C, TMSCN (0.604 g, 3.39 mmol) was added, and the resulting mixture was stirred for 10 h at room temperature. Evaporation of the solvent gave a residue which was submitted to flash chromatography. Elution with light petroleum/AcOEt (4:1) afforded **23** as an inseparable mixture of two major (2*S*)- and two minor (2*R*)-aminonitriles (0.280 g, 37%); $^1$H NMR (400 MHz): $\delta = 1.90$–2.00 (m, 1H, 4′-$CH_a$ of major + minor isomers), 2.15–2.19 (m, 1H, 5′-$CH_a$ of minor isomer), 2.18–2.24 (two dd partially overlapping, $J = 3.0$ and 7.0 Hz, 1H, 5′-$CH_a$ of major isomers), 2.29 (d, $J = 3$ Hz, 1H, 5′-$CH_b$ of a major isomer), 2.34–2.38 (m, 1H, 5′-$CH_b$ of a major isomer + two minor isomers), 2.80–2.88 (m, 1H, 5′-$CH_b$ of two major + a minor isomers), 2.90 (dd, $J = 3.0$ and 10.0 Hz, 1H, 5′-$CH_b$), 3.47–4.08 (m, 7H, $COCH_3$, C$H_2$OH, C*H*Ph and CHCN of all isomers), 4.34 (d, $J = 7.0$ Hz, CHCl of a major isomer), 4.37 (d, $J = 7.0$ Hz, CHCl of a major isomer), 4.42–4.46 (two d partially overlapping, $J = 7.0$ Hz, CHCl of the two minor isomers), 7.25–7.40 ppm (m, 5H, aromatics of all isomers); $^{13}$C NMR (100 MHz): $\delta =$ 43.98, 44.02, 45.10, 45.14, 45.26, 45.41, 45.71, 45.86, 45.97, 46.03, 46.10, 46.17, 46.25, 46.59, 46.84, 47.24, 62.89, 63.04, 63.13, 63.41, 66.61, 66.69, 67.17, 67.24, 68.51, 68.72, 68.92, 69.10, 117.05, 117.10, 117.29, 117.43, 127.46, 127.50, 127.59, 128.42, 128.86, 128.95, 137.56, 137.82, 139.15, 166.78, 166.86 ppm.

**2-(2′-Chloro-3′-carboxybicyclo[1.1.1]pentyl)glycine (12)**: Lead(IV) acetate (0.286 g, 0.64 mmol) was added to a cold (0 °C) magnetically stirred solution of **23** (0.180 g, 0.53 mmol) in dry $CH_2Cl_2$/MeOH (6 mL, 2:1). After 10 min, the cooling bath was removed, and stirring continued for 20 min. Water (12 mL) was then added, and the resulting mixture was filtered with the aid of celite. The organic phase was separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2×10 mL). The combined organic phases were dried over anhydrous $Na_2SO_4$, filtered, and the solvent evaporated off to afford a residue (0.180 g) which was heated at reflux in 6 N HCl (12 mL) for 12 h. After cooling, the reaction mixture was washed with $CH_2Cl_2$ (5 mL) and evaporated to dryness. The residue was

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submitted to ion-exchange chromatography on Dowex 50WX2-200. Elution with 10% pyridine afforded **12** as a mixture of a major and a minor racemate (0.094 g, 79%); $^1$H NMR ($D_2O$, 400 MHz): $\delta =$ 1.81 (dd, $J = 3.0$ and 10.0 Hz, 1H, 4′-$CH_a$ major isomer), 1.87 (dd, $J =$ 3.0 and 10.0 Hz, 1H, 4′-$CH_a$ minor isomer), 2.02–2.06 (two dd partially overlapping, 1H, $J = 3.0$ and 7.0 Hz, 5′-$CH_a$ of both isomers), 2.25 (d, $J = 3.0$ Hz, 1H, 5′-$CH_b$ major isomer), 2.30 (d, $J = 3.0$ Hz, 1H, 5′-$CH_b$ minor isomer), 2.74 (dd, $J = 3.0$ and 10.0 Hz, 1H, 4′-$CH_b$ major isomer), 2.78 (dd, $J = 3.0$ and 10.0 Hz, 1H, 4′-$CH_b$ minor isomer), 3.79 (s, 1H, 2-CH, minor isomer), 3.80 (s, 1H, 2-CH, major isomer), 4.32 (d, $J = 7.0$ Hz, 1H, CHCl minor isomer), 4.35 ppm (d, $J = 7.0$ Hz, 1H, CHCl, major isomer); $^{13}$C NMR ($D_2O$, 100 MHz): $\delta =$ 43.14, 43.30, 44.51, 44.73, 45.59, 45.71, 46.01, 46.74, 52.26, 69.06, 69.81, 170.39, 172.69 ppm.

**Molecular modeling**: Ligands were built by using the sketch module of Cerius-2.[24] Each compound was minimized with the Universal force-field v1.2 and the Smart Minimizer protocol of the Open Force Field module (OFF).[25] Atomic charges were calculated by using the semiempirical Mopac/AM1 method. Docking experiments were performed with AutoDock v3.0.[23] Briefly, six experiments of 300 docking runs were carried out by using the genetic algorithm with a population size of 50 individuals and 2500000 energy evaluations. Other parameters were left at their respective default values. The search was conducted in a grid of 60 points per dimension and a step size of 0.375 centered on the coordinates of the $C^\alpha$ atom of glutamate, as resulting in the binding conformation of the crystal structure. All calculations were carried out on SGI O2 R5000 and R10000 workstations.

**NMDA-induced convulsion in mice**: NMRI mice (22–24 g, Charles River, $n = 8$ per group) were subjected to icv infusion of NMDA into the third ventricle by using the reported freehand technique.[26] In brief, conscious mice were positioned under an infusion needle with the orbital arch and midline sagital line as reference positions. Following freehand positioning of the infusion needle into the third ventricular (descending point 3.4 mm from skin surface), infusion was started with a microinfusion pump (CMA). A flow-rate of 4 μL min$^{-1}$ was used to infuse either saline (NMDA vehicle) or NMDA (15 ng μL$^{-1}$) for a maximum of 75 s (cutoff time). The time to clonic convulsions was recorded and if no convulsions were observed, the cutoff value was noted at 75 s. All mice were icv pretreated 30 min prior to icv infusion with either saline or test compound (2 μL). Statistical analysis was performed with one-way ANOVA on ranks with Dunn's post test.

**Keywords:** bicyclo[1.1.1]pentane · group I mGluR antagonists · neurochemistry · polycycles · receptors

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