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Asymmetric synthesis of some substituted-3-phenyl prolines

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Abstract

The asymmetric synthesis of carboxyphenyl prolines was performed according to Schöllkopf methodology, to prepare possible antagonists of the metabotropic glutamate receptor mGluR1. © 1999 Elsevier Science S.A. All rights reserved.

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During the last 15 years, glutamate has become recognized as the main excitatory neurotransmitter within the mammalian central nervous system (CNS), playing different and fundamental roles in many different aspects of the functioning of the CNS. The action of glutamate occurs through both ionotropic receptors (iGlu), that is through the activation of receptor-gated cation channels (namely AMPA, Kainate and NMDA), and through metabotropic receptors (mGlu), which are seven transmembrane (7-TM) receptors coupled to G-proteins [1]. The mGlu receptor family is actually quite unusual, while retaining the characteristic structural features of G-proteins coupled receptors—the seven transmembrane domains—the members of this family possess a huge N-terminal extracellular domain, in which the glutamate binding site is thought to be located [2,3]. The mGluRs family can be conveniently divided into three groups on the basis of their sequence homology and pharmacological behavior. Group I (mGluR1 and R5) is positively coupled to phospholipase C (PLC) while Group II (mGluR2 and R3) and Group III (mGluR4,R6,R7 and R8) are negatively coupled to adenilate cyclase (AC) [4]. Although site-directed mutagenesis studies and molecular modeling techniques shed some light on the theories concerning the glutamate recognition domain on mGluRs receptors, still relatively little is known about the interaction of the binding sites with their ligands known in literature [3].

The search for potential novel agonists/antagonists at the mGlu receptors was mainly towed by the synthesis of a large number of phenylglycine derivatives which showed some signs of potential interest even if their receptor selectivity (among the different groups) is sometimes not very high [5]. Some of the products acting at the different receptors are depicted in Fig. 1. As far as Group I receptors are concerned, the synthesis of a potential antagonist could reveal interesting therapeutic potentials for these products, literature studies show that these molecules could be useful in tackling different pathologies such as strokes, neurodegeneration, Parkinson's disease, and pain [6].

Many academic researchers and pharmaceutical companies are now involved in mGluR1 selective antagonists synthesis as shown by the large number of patents and publications. Recently, Eli Lilly tried to mimic CPGs replacing the phenolic component of 4C,3H-CPG (**3**) with an indole ring [7], but unfortunately none of the two derivatives proposed (**6** and **7**, depicted in Fig. 2) were active as a mGluR1 antagonist up to a concentration of 100 mM.

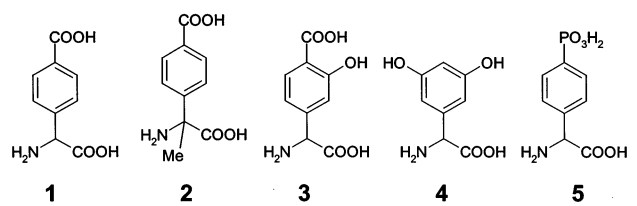

Fig. 1. Some of the known antagonist/agonist for the mGluRs family: 4-CPG (**1**), MCPG (**2**), 3H-4-CPG (**3**), 3,5-dihydroxy CPG (**4**) and 4-PPG (**5**).

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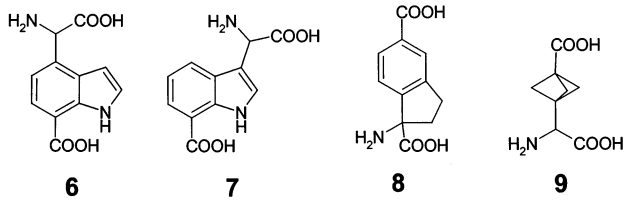


Fig. 2. Eli Lilly indolo CPG analogs (**6**, **7**), AIDA (**8**) and UPF 596 (**9**).

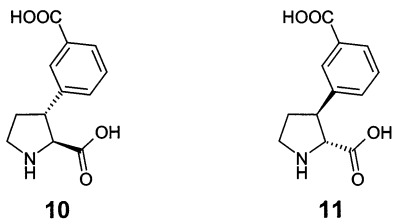


Fig. 3. (*S*)-(3-Carboxyphenyl)-3-proline (**10**) and (*R*)-(3-carboxyphenyl)-3-proline (**11**).

A huge amount of work to modify and replace the skeleton of the CPGs was done by Professor Pellicciari's group at the University of Perugia. In the derivative AIDA (**8**, Fig. 2), the aminoacidic moiety was cyclized with the phenyl ring giving rise to a very selective mGluR1 antagonist [8]. Moreover, the same research group showed that the phenyl ring was not fundamental to the activity of the CPG synthesizing UPF 596 (**9**, Fig. 2) in which a propellane ring replaced the aromatic moiety [9]. As reported by these authors, the use of molecular modeling would predict that the derivative **9** may interact with the described putative pharmacophoric points in the extracellular part of the mGluR1 receptor, even if it is considerably shorter than the corresponding 4-CPG derivative [3]. The theory underlying the synthesis of these derivatives proposes that not only a certain distance between the aminoacidic group and the carboxylic moiety, but also a certain degree of linearity is necessary between them in order

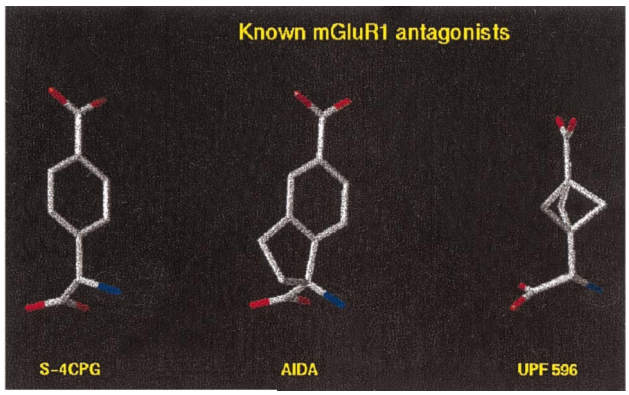


Fig. 4. Minimized conformers of known mGluR1 antagonists ((*S*)-4-CPG, AIDA, UPF 596).

to obtain molecules active at the mGluR1 site. As a tool to test this hypothesis we synthesized (*S*)-(3-carboxyphenyl)-3-proline (**10**, Fig. 3). This derivative and its corresponding enantiomer (**11**, Fig. 3) are depicted in Fig. 3.

These molecules were submitted to a conformational analysis within Sybyl in order to take account of their rotable bonds [10] and the different conformers obtained were minimized. The same work was performed on the three known antagonists depicted in Fig. 4.

The conformer endowed with the lower energy of (*S*)-(3-carboxyphenyl)-3-proline (**10**), has with the correct distance between the carboxy group on the aromatic moiety and the aminoacidic group to superimpose with 4-CPG and AIDA. Obviously it cannot be superimposed with the 'shorter' UPF 596 as depicted in Fig. 5(D).

It can also be clearly observed that the product **10** is not endowed with the supposed required linearity between the aminoacidic moiety and the carboxylic group and that the two aromatic regions only partially overlap.

The synthesis of this derivative was performed in accordance with that described for the unsubstituted

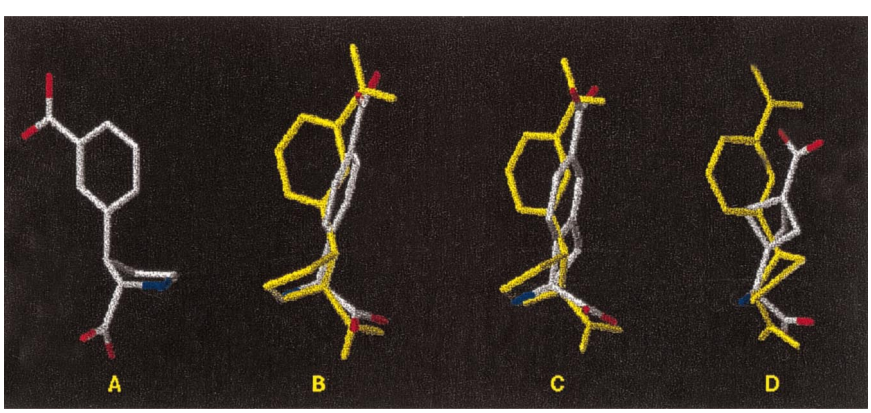
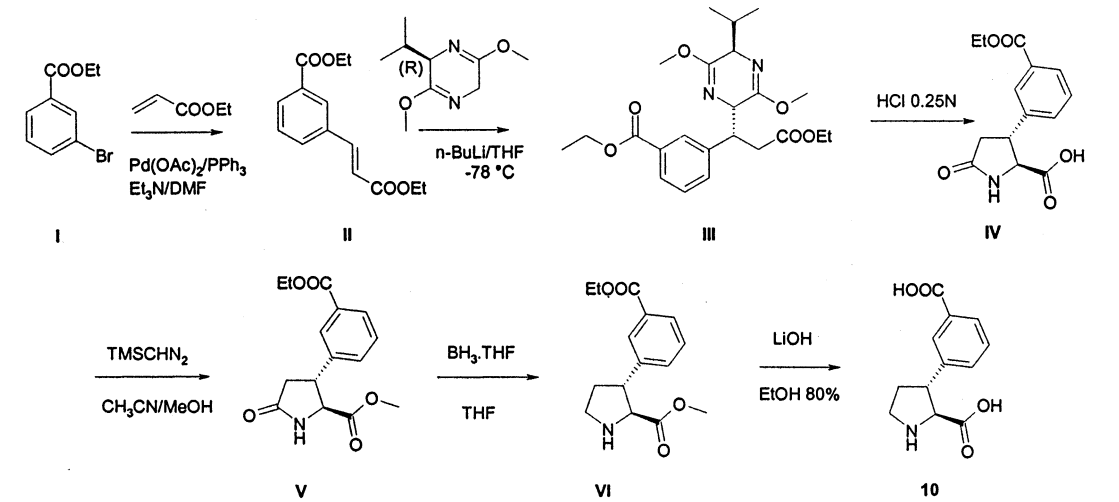
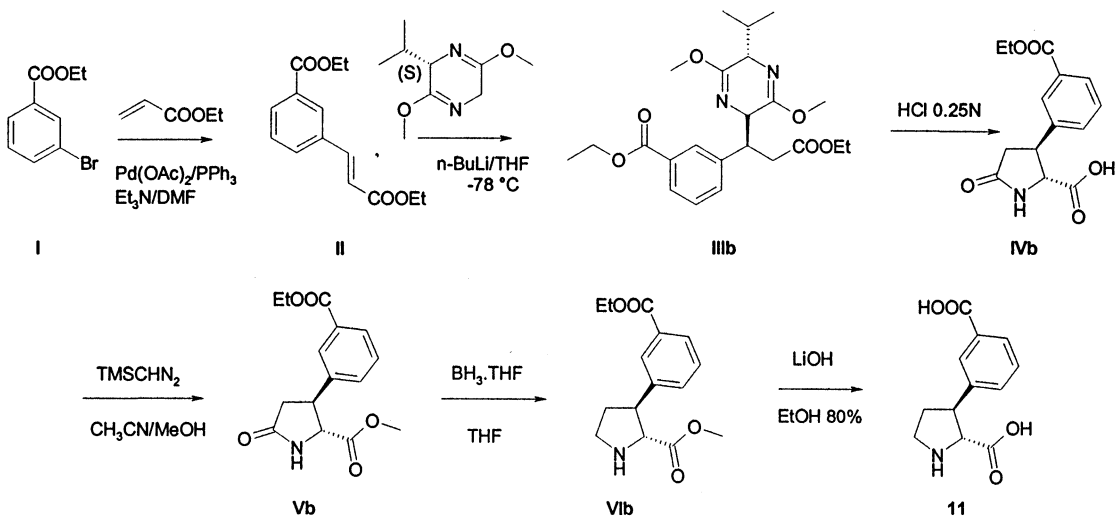


Fig. 5. Superimposition of the lower energy conformer of derivative **10** (A) with (*S*)-4-CPG (B), AIDA (C) and UPF 596 (D).



Scheme 1.



Scheme 2.

cinnamate in the literature by Schöllkopf et al. [11] and is outlined in Scheme 1.

The 3′-ethoxycarbonylcynnamate (**II**), which was easily prepared via Heck reaction in high yield, was subjected to attack by the commercially available (*R*) *i*-propyl Schöllkopf reagent in dry THF under nitrogen at −78°C to give intermediate **III** in 50% yield as single product. The bis lactim derivative was hydrolyzed with 0.25 N HCl and the corresponding aminoacid derivatives underwent an in situ cyclization to give the corresponding lactam **IV** which was recovered in 60% yield after purification by flash chromatography. Protection of the free carboxylic group with TMS–CHN_2 produced the protected derivative **V** in quantitative yield. The chemoselective reduction of the γ-lactam with borane–dimethyl sulfide complex (6 equiv.) in refluxing THF produced the intermediate **VI** in 70% yield (no trace of the alcohol derived from a possible reduction of the ethoxycarbonyl group was observed) [12,13]. The final hydrolysis with hydrated lithium hydroxide in aqueous ethanol gave complete conversion to the aminoacidic desired product **10** in high yield after desalting.

The case reported here is the first in which an ethoxycarbonyl substituted cinnamate is used as a Michael acceptor with the Schöllkopf reagent. The complete stereoselectivity of the attack can be explained according to Schöllkopf's notes on acrylates [11] and it is noteworthy that the presence of a second carbonyl group on the aromatic moiety of the cinnamate probably does not modify the proposed transition state [11].

In order to give chemical completion to this work, the corresponding enantiomer **11** was also synthesized as reported in Scheme 2. The enantiomeric purity for both the enantiomers (**10** and **11**) were derived from the results of chiral shift NMR techniques on both **VI** and **VIb**. The tabulated spectra for compound **10** (**11**) and the experimental conditions used for **VI** and **VIb** are reported in the

footnote[1]. The possible racemization in the final step was excluded once more with the help of NMR techniques (in the case of racemization, *syn* products should have been observed through *Jcis*).

The derivative **10** and its enantiomer **11** were tested in CHO cells expressing rat-mGluR1 receptor, but unfortunately none of them showed activity up to the concentration of 10 mM. This could be in accordance with the above-described theory [3] and with the lack of linearity between the two moieties involved within the recognition of the putative pharmacophoric points, but the inactivity could also be due to a degree of rotation around the phenyl rotable bond greater than that expected by MM calculation. To solve this problem for definite, further work is in progress on more rigid derivatives.

Acknowledgements

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[1] Compound **10** (**11**): ^{1}H NMR (500 MHz, ppm, DMSO-d_6): 13.0 (1H, bs), 8.90 (2H, bm), 7.94 (1H, m), 7.80 (1H, d), 7.62 (1H, d), 7.44 (1H, t), 3.67 (1H, d, $J = 7.5$ Hz), 3.48 (1H, m) 3.3–3.1 (m, 2H), 2.3 (1H, m), 1.9 (1H, m). The enantiomeric purity of **VI** and **VIb** was determined at 500 MHz using chiral lanthanide shift reagents. Significant splitting of the aromatic ($\Delta\delta = 8$ Hz) and CH (3.6 ppm) ($\Delta\delta = 9$ Hz) signals of the enantiomers was obtained in $CDCl_3$ solution, at 28°C, with Eu(-dpm)$_3$(tris[dipivaloylmethanate]europium(III)).