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ASYMMETRIC SYNTHESIS OF ENANTIOMERICALLY PURE (2*S*,1'*S*,2'*S*,3'*R*)-PHENYLCARBOXYCYCLOPROPYLGLYCINE (PCCG-4): A POTENT AND SELECTIVE LIGAND AT GROUP II METABOTROPIC GLUTAMATE RECEPTORS

Maura Marinozzi,[a] Benedetto Natalini,[a] Gabriele Costantino,[a] Pierre Tijskens,[a] Christian Thomsen,[b] Roberto Pellicciari,*[a]

[a] *Istituto di Chimica e Tecnologia del Farmaco, Università di Perugia, Via del Liceo, 1- 06123 Perugia (Italy)*

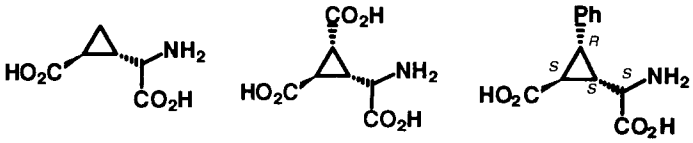
[b] *Health Care Discovery, Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv (Denmark)*

Abstract: The enantioselective synthesis of (2*S*,1'*S*,2'*S*,3'*R*)-2-(2'-carboxy-3'-phenylcyclopropyl) glycine (PCCG-4, **3**), a potent and selective mGluR2 antagonist is described.

The pharmacological characterization of G-protein coupled metabotropic glutamate receptors (mGluRs) is currently the object of intense studies. Indeed this excitatory receptor family has been shown to be involved in important CNS functions such as the long term potentiation (LTP) of memory as well as in a number of neurodegenerative and psychiatric disorders.[1] Eight mGluRs subtypes (mGluR1-mGluR8) have so far been expressed and subdivided in three groups according to coupling to signal transduction pathways and to amino acid sequence homology: Group I mGluRs (mGluR1 and mGluR5) are coupled to PI/Ca^{2+} cascade, while Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, mGluR8) mGluRs are negatively coupled to adenylyl cyclase.[2]

The mGluRs ligands so far developed have been of great help in delineating the physiological role and the therapeutic potential of each mGluRs group. Thus, it is now accepted that activation of Group I mGluRs results in an exacerbation of neurotoxic effects while activation of Group II and Group III mGluRs leads to neuroprotective effects.

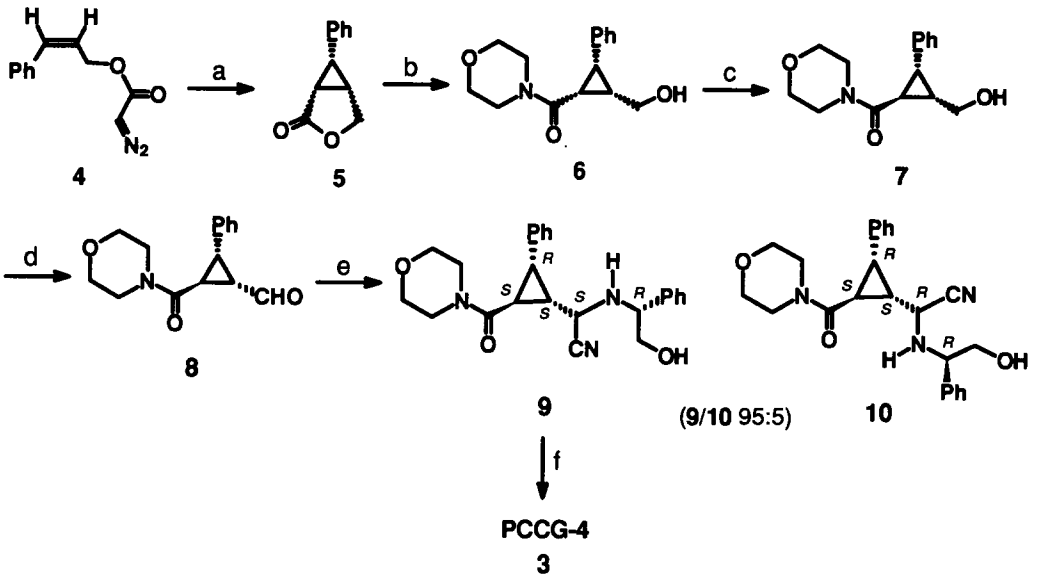
Among the ligands currently used to characterize mGluRs, carboxycyclopropylglycine (CCG) derivatives such as L-CCG I (**1**)[3] and DCG IV (**2**)[4] are playing an important role in the evaluation of the physiological and pharmacological properties of Group II mGluRs. As a part of a project aimed at finding new CCG derivatives as potent and selective mGluRs ligands we have recently prepared a complete stereolibrary of all the sixteen 2-(2'-carboxy-3'-phenylcyclopropyl)glycine (PCCG) diastereoisomers by an enantiodivergent synthesis involving the $Cu(TBS)_2$ catalyzed cyclization of suitable allylic diazoacetates.[5] Among these diastereoisomers, (2*S*,1'*S*,2'*S*,3'*R*)-2-(2'-carboxy-3'-phenylcyclopropyl)glycine (PCCG IV, **3**) was able to antagonize, with an IC_{50} of 8 μM, the effects of glutamate on forskolin-induced cAMP formation in BHK cells expressing mGluR2. It showed also no activity for ionotropic and PI-coupled metabotropic glutamate receptors, thus proving to be a potent and selective group II mGluRs antagonist.



CCG I **1** DCG IV **2** PCCG IV **3**

In view of the relevance of PCCG IV (**3**) as a novel and promising tool for the understanding of the physiological role played by group II mGluRs, we have undertaken its enantioselective synthesis (Scheme 1). The key optically active intermediate on route to PCCG IV(**3**) has been the (1*S*,2*S*,3*R*)-morpholine amide **7** which has been prepared by the enantioselective intramolecular cyclopropanation of *cis*-3-phenyl-2-propen-1-yl diazoacetate (**4**)[6] catalyzed by $Rh_2(5S\text{-MEPY})_4$ (66%)[7] and followed by opening of the (1*R*,5*S*,6*R*)-lactone **5** (ee. 92%)[8] (morpholine, $AlMe_3$, 90%).[9] Selective epimerization [$LiN(SiMe_3)$, THF, 99%][10] of the morpholinocarbonyl moiety of the (1*R*,2*S*,3*R*)-amide **6** followed by oxidation of the primary alcoholic function of **7** with PCC gave the (1*S*,2*S*,3*R*)-aldehyde **8** with 50% yield. A diastereoselective Strecker synthesis involving the condensation of aldehyde **8** with optically active *R*-(-)-α-phenylglycinol[11] (MeOH, rt, 2 h) followed by nucleophilic addition of a cyanide ion to the Schiff base (TMSCN, 0 °C, then rt, 12 h) afforded the (2*S*,1'*S*,2'*S*,3'*R*)-aminonitrile **9** along with minor amounts of the (2*R*,1'*S*,2'*S*,3'*R*)-aminonitrile **10** (95:5, gc-mass spectrometry). Separation of the two aminonitriles **9** and **10** by medium pressure chromatography (mpc) (light petroleum-AcOEt, 8:2) afforded the more abundant diastereoisomer **9** (51% yield) which was oxidized by lead tetraacetate (CH_2Cl_2-MeOH, 0 °C, 10 min) and then submitted to acidic (6N HCl) hydrolysis, ion exchange resin chromatography (Dowex 50WX2-200, 10% Py) and reversed phase (rp-8) mpc (H_2O-MeOH, 15:5) to afford PCCG IV (**3**)[12] (75%) with 11% overall yield from **4**.

Scheme 1



a) $Rh_2(5S\text{-MEPY})_4$, CH_2Cl_2, reflux; b) Morpholine, $AlMe_3$, CH_2Cl_2, reflux; c) Li-HMDS, THF, rt;
d) PCC, CH_2Cl_2, rt; e) i. *R*-α-phenylglycinol, MeOH, rt; ii.TMSCN, 0 °C, then rt; iii. mpc;
f) i. $Pb(OAc)_4$, CH_2Cl_2-MeOH (1:1), rt; ii. 6N HCl, reflux; iii. Dowex 50WX2-200, 10% Py; iv. rp8-mpc

The synthetic methodology above reported provides efficient access to PCCG-4 (**3**), a novel and useful tool for delineating the physiological roles of group II mGluRs in the CNS. Studies in this direction are currently under way in our laboratories and the results will be reported in due time.

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8 The enantiomeric excess of the lactone **5** was measured by integration of the enantiotopic peaks in the ^{1}H-NMR spectrum [C_6D_6, Eu(tfc)$_3$] of the corresponding diol obtained by reaction of **5** with methyllithium .[10]
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12. Analytical data for new compounds **8**, **9** and **3**:
    8: mp 89-91 °C; ^{1}H-NMR ($CDCl_3$) δ 2.85 (1H, m, *CH*CHO), 3.12 (1H, t, J=6.4 Hz, CHCON), 3.30 (1H, dd, J=6.4 and 9.4 Hz, *CH*Ph), 3.50-3.80 (8H, m, morpholine ring), 7.18-7.40 (5H, m, aromatics), 9.18 (1H, d, J=5.1 Hz, CHO); $[\alpha]_D^{20}$ +8.2 (c 0.45, CH_2Cl_2)
    9: mp 147-8 °C; ^{1}H-NMR ($CDCl_3$) δ 2.20 (3H, m, 1'-CH, 2'-CH and OH), 2.61 (1H, d, J=8 Hz, 2-CH), 2.90 (1H, m, 3'-CH), 3.50-4.05 (11H, m, morpholine, CH_2OH and *CH*CH_2OH), 6.90-7.40 (10H, 2xm, aromatics); ^{13}C-NMR ($CDCl_3$) δ 22.87, 29.89, 42.77, 46.16, 62.94, 66.72, 118.80, 127.23, 127.57, 128.23, 128.56, 128.71, 134.00, 138.34, 169.20; $[\alpha]_D^{20}$ -151 (c 0.19, CH_2Cl_2)
    3: mp 217-8 °C; ^{1}H-NMR (D_2O+DCl) δ 2.15 (1H, ddd, J=5.2, 9.3 and 11.2 Hz, 1'-CH), 2.49 (1H, t, J=5.2 Hz, 2'-CH), 3.05 (1H, dd, J=5.2 and 9.3 Hz, 3'-CH), 3.20 (1H, d, J=11.2 Hz, 2-CH), 7.30 (5H, m, aromatics); ^{13}C-NMR (D_2O+DCl) δ 22.91, 27.76, 31.33, 51.51, 127.66, 128.57, 128.95, 133.27, 169.69, 175.27; $[\alpha]_D^{20}$ -108 (c 0.15, 2.5N HCl).

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