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A Novel Class of Antagonists for Metabotropic Glutamate Receptors, 7-(Hydroxyimino)cyclopropa[b]chromen-1a-carboxylates

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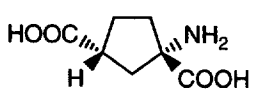
Abstract : 7-(Hydroxyimino)cyclopropa[b]chromen-1a-carboxylates (**4a-c**), highly potent antagonists for a phospholipase C-linked metabotropic glutamate receptor, mGluR1, were synthesized through cyclopropanation onto 4-oxo-4H-1-benzopyran-2-carboxylates (**5a-c**) utilizing dimethyloxosulfonium methylid followed by treatment with hydroxylamine.

Metabotropic glutamate receptors (mGluRs) have been identified as a family of excitatory amino acid receptors coupled to intracellular signal transduction via G-proteins.[1] The recent molecular cloning studies[1b,d,e,2] have revealed that mGluRs consist of eight subtypes, termed mGluR1 to mGluR8, which can be classified into three broad subgroups on the basis of sequence similarity, signal transduction mechanism, and agonist selectivity. The first group includes mGluR1 and mGluR5, both of which are positively coupled to phospholipase C and hydrolysis of phosphatidylinositol. The second group that consists of mGluR2 and mGluR3 is negatively coupled through adenylate cyclase to inhibition of c-AMP. The third group, including mGluR4, mGluR6, mGluR7 and mGluR8, is also linked to inhibition of c-AMP but the agonist selectivity markedly differs from that of the second group. Although selective agonists and antagonists for mGluRs have been reported such as trans-ACPD[3a,b] (**1**), a series of 2-(carboxycyclopropyl)glycine (L-CCG-I)[3c,d] **2a**, its derivatives (DCG-IV[3e,f] **2b** and MCCG[1f] **2c**) and a series of 2-(carboxyphenyl)glycines[1f,3g] [(S)-4CPG **3a** and (RS)-MCPG **3b**], it is still required to develop potent agonists and antagonists with selectivity for the different subtypes or subgroups to investigate the role of mGluRs in the mammalian central nervous system.[4]

In this communication, we report the synthesis of 7-(hydroxyimino)cyclopropa[b]chromen-1a-carboxylates (**4a-c**), a structurally novel class of antagonists for a phospholipase C-linked metabotropic glutamate receptor such as mGluR1.



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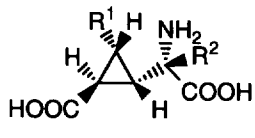
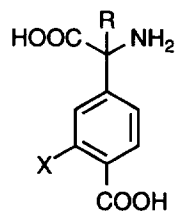
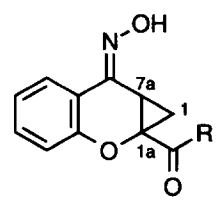


2a (R^1=R^2=H)
2b (R^1=COOH; R^2=H)
2c (R^1=H; R^2=Me)



3a (R=H; X=OH)
3b (R=Me; X=H)

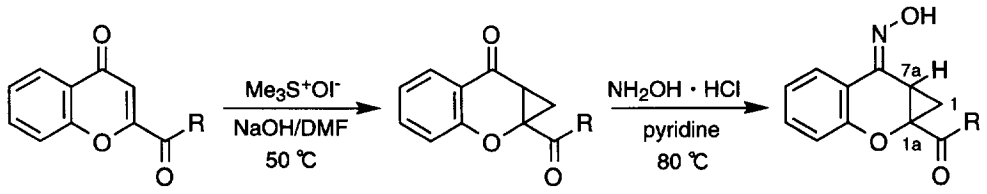


4a (R=OEt)
4b (R=NHPh)
4c (R=NMePh)

Chemistry

A survey of literature has revealed that a few methods[5] involving carbene spieces for the construction of the cyclopropa[b]chromen-1a-carboxylate skeleton are reported. However, they are only limited to the 1-substituted cyclopropane derivatives and inapplicable to the synthesis of **4a-c**. After extensive experiments, we found that, upon treatment with Corey's dimethyloxosulfonium methylid[6] generated from trimethylsulfoxonium iodide with NaOH in DMF, 4-oxo-4H-1-benzopyran-2-carboxylates[7] (**5a-c**) underwent the cyclopropanation to produce the adducts **6a-c** in good yields.[8]

Scheme 1



5a (R=OEt)
5b (R=NHPh)
5c (R=NMePh)

6a (R=OEt) (45%)
6b (R=NHPh) (50%)
6c (R=NMePh) (67%)

4a (R=OEt) (68%)
4b (R=NHPh) (86%)
4c (R=NMePh) (82%)

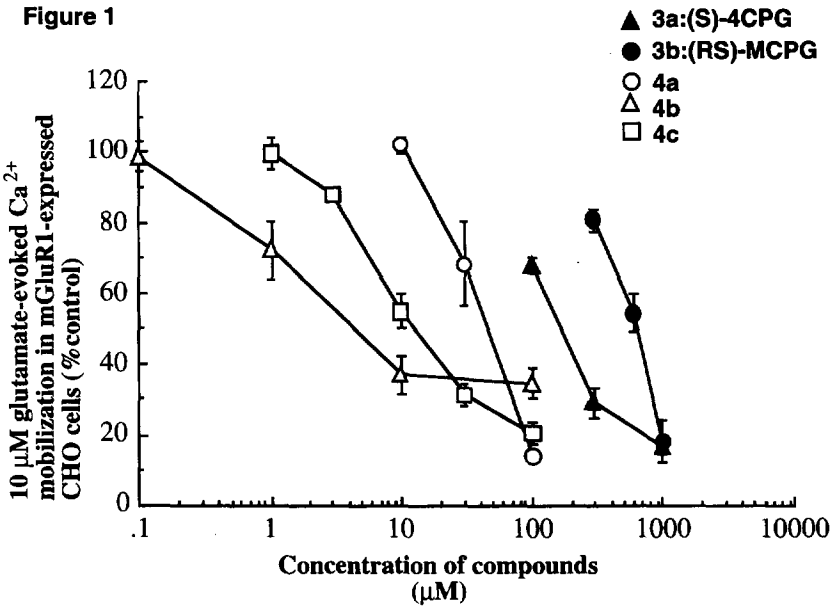
The reactions of **6a-c** with hydroxylamine hydrochloride in pyridine gave **4a-c** accompanied by a small amounts of the geometric isomers on the oxime moiety (>20:<1) which could be easily separated by column chromatography over silica gel (hexane:ether=5:3). The stereochemistries of the oxime moiety of **4a-c** were determined to be E-configuration by comparison of their NMR data with those of the geometric Z-isomers. For instance, in the ^{1}H-NMR (270 MHz, $CDCl_3$) of **4a**,[9] the signal of the C-7a methine proton appeared at δ 3.38 (dd, J=10.56 and 7.26 Hz) and this was shifted lower field than that of the geometric isomer[10] (δ 2.85, dd, J=10.56 and 7.26 Hz) by anisotropic effect of the oxygen atom on the oxime moiety. Fortunately, recrystallization (hexane/ether) of the mixture gave only the E isomer **4a-c** in the yield shown in Scheme 1.

Results and Discussion

The effects of a series of the synthetic compounds **4a-c**, **5a-c** and **6a-c** for mGluR1 were evaluated by measuring Ca^{2+} mobilization in response to 10 μM glutamate in mGluR1α-expressed CHO cells.[2a,c] Consequently, **4a-c** were found to be highly potent antagonists whose IC_{50} values were 23 μM, 3 μM and 10 μM, respectively. As shown in Figure 1, **4a-c** inhibit in a dose-dependent manner and act as more powerful antagonists than the known 2-(carboxyphenyl)glycines [(S)-4CPG **3a**, IC_{50}=200 μM; (RS)-MCPG **3b**, IC_{50}=700 μM] which are adopted as reference standard[11] for mGluR1 antagonists. In particular, the anilide derivative **4b** shows a 67-fold higher potency as compared with (S)-4CPG (**3a**). The compounds **4a-c** were not partial agonists since no effects on basal Ca^{2+} mobilization was observed by themselves at the concentration 1 to 100 μM. The characteristic feature of **4a-c** is the presence of a cyclopropane ring and an oxime group that is essential for the antagonist activities since **5a-c** and **6a-c** did not show any effects. Furthermore, the ester **4a** did not show any agonist and antagonist activities at ionotropic glutamate receptors [*N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) and kainate (KA) receptor subtypes] in *Xenopus* oocyte injected with rat brain[12] and the adenylate cyclase-linked mGluR2[2b] at the concentration up to 100 μM. A 100 μM of **4a** completely inhibits on 10 μM glutamate-

evolved Ca^{2+} mobilization in mGluR5-CHO cells.[2d] Therefore, the oximes **4a-c** can be expected to be highly potent and selective antagonists for mGluR1 and mGluR5, the subtypes linked to the phosphatidyl-inositol hydrolysis, although further data are necessary to clarify their precise pharmacological profile.

Figure 1



In conclusion, we described a facile and practical method for the synthesis of 7-(hydroxyimino)-cyclopropa[b]chromen-1a-carboxylates (**4a-c**) which act as highly potent antagonists at the phospholipase C-linked receptor, mGluR1. To our knowledge, **4b** is the most potent antagonist for mGluR1 reported to date. The compounds **4a-c** would be useful tools to investigate the role of mGluRs in the mammalian central nervous system and their possible involvement in pathophysiological process. A more detailed data including the selectivity for each subtype and the structure-activity relationship of these compounds will be reported in due course.

Acknowledgement

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References and Notes

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4. After we presented this study at *AFMC International Medicinal Chemistry Symposium* in Tokyo, September 3-8, **1995** (abstract p.79), Pellicciari *et al.* reported that 1-aminoindan-1,5- dicarboxylic acid, a confomationally constrained 2-(carboxyphenyl)glycine analogue, is a potent antagonist for mGluR1: Pellicciari, R.; Luneia, R.; Costantino, G.; Marinozzi, M.; Natalini, B.; Moroni, F.; Thomsen, C.; *J. Med. Chem.* **1995**, *38*, 3717.
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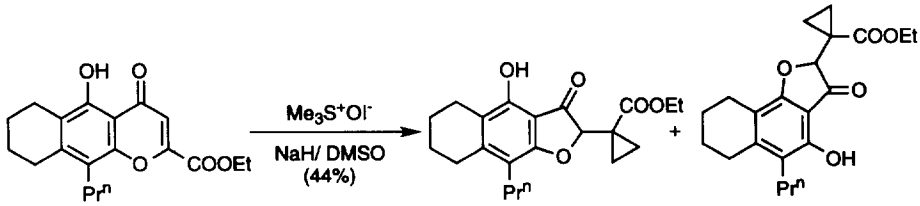
8. In contrast to our results, Suschitzky *et al.* reported that the similar reaction of the 4-oxo-4H-1-benzopyran-2-carboxylate (**I**) bearing a hydroxy group at the benzene ring did not give the cyclopropanated products but yielded the benzofuran derivatives (**IIa,b**).[5b]



I **IIa** **IIb**

9. **4a**: ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.35 (3H, t, J=7.26 Hz), 1.49 (1H, m), 2.05, (1H, dd, J=10.56 and 5.95 Hz), 3.38 (1H, dd, J=10.56 and 7.26 Hz), 4.28 (2H, q, J=7.26 Hz), 6.98 (1H, d, J=7.92Hz), 7.03 (1H, d, J=8.58 Hz), 7.32 (1H, m), 7.51 (1H, s, OH, exchangeable with D_2O), 7.74 (1H, dd, J=7.92 and 1.32 Hz).
10. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.35 (3H, t, J=7.26 Hz), 1.49 (1H, m), 1.84, (1H, dd, J=10.56 and 5.95 Hz), 2.85 (1H, dd, J=10.56 and 7.26 Hz), 4.32 (2H, q, J=7.26 Hz), 7.04 (1H, d, J=7.92Hz), 7.09 (1H, d, J=8.58 Hz), 7.37 (1H, m), 8.44 (1H, dd, J=7.92 and 1.32 Hz), 8.92 (1H, brs, OH, exchangeable with D_2O).
11. (S)-4CPG (**3a**) acts not only as an antagonist at mGluR1 but also as a week agonist at mGluR2. (RS)-MCPG (**3b**) is a nonselective antagonist for mGluR1 and mGluR2: See ref. 1f, 3g.
12. Sugiyama, Y.; Ito, I.; Hirono, C.; *Nature* **1987**, *325*, 531.

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