Coumarin derivatives as monoamine oxidase B inhibitors with antiparkinsonian like properties

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Introduction
Parkinson disease (PD) is the second most common neurodegenerative disorder causing progressive disability1. One therapeutic option for treatment of PD is the use of monoamine oxidase B (MAO-B) inhibitors in monotherapy or concomitantly with levodopa2. Some coumarin compounds have shown selective inhibition of MAO-B3,4,5. In this study, monoamine oxidase inhibitory activity and the possible antiparkinsonian effects of coumarin derivatives were evaluated.

Methods
Two coumarin derivates (CD1 and CD2) were synthesized and evaluated in following tests:
• In vitro assay of MAO inhibition
  Monoamine oxidase inhibitory activity of CD1 and CD2 were evaluated using the Amplex® Red kit (Molecular Probes, Eugene, Oregon, USA) and the recombinant human isoforms A and B (Sigma-Aldrich).
• In vivo assay of 2-phenylethylamine (PEA)
  The mice were administered with selegiline (10 mg/kg), vehicle, CD1 or CD2 in doses of 50, 100 and 200 mg/kg. Then PEA was administrated, and stereotyped behavior produced or increased by PEA were scored on a 0-4 scale depending on the intensity of the behavior exhibited
• Reserpina model
  The reversal of the hypokinesia produced by reserpine in mice was evaluated in open field, after administration of vehicle, selegiline (10 mg/kg), CD1 or CD2 in doses of 50, 100 and 200 mg/kg.

Results
• In vitro assay of MAO inhibition
  The results showed that both coumarin compounds presented selective inhibitory activity towards MAO-B (IC50 values: CD1=5.46 ± 0.36 µM and CD2 =41.63 ± 2.79 µM)
• In vivo assay of 2-phenylethylamine (PEA)
  Stereotyped behavior in mice after administration PEA, in combination with CD1 or CD2, suggests in vivo inhibition of MAO-B for this compounds

Fig.1 Stereotyped behavior in mice after administration PEA (23 mg/kg) in combination with CD1 (100 mg/kg), CD2 (100 mg/kg), vehicle (0.1 mL/10 g) or selegiline (10 mg/kg). * Significant difference with respect control group (p<0.05).

• Reserpina model
  Compounds CD1 and CD2 produced a significant increase in the locomotor activity of reserpinized mice compared to the control group.

Fig.2 Motor activity of reserpinized mice (3 mg / kg) that received CD1 (100 mg/ kg), CD2 (100 mg/kg), selegiline (10 mg / kg) or vehicle. * Significant difference with respect control group (p<0.05).

Conclusion
Coumarin derivates CD1 and CD2 presented selective inhibitory activity on monoamino oxidase B and anti-parkinsonian effects in a model of PD. Therefore, they could be potential antiparkinsonian agents.

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References