Rimonabant Multiple Ligands Targeting CB and PPAR Receptors

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Background. Rimonabant, the first CB1 antagonist launched as appetite suppressant had to be withdrawn due to its side effects. However, the ECS is still an interesting target for obesity [1] and there is a lot of research carried out looking for peripheral acting compounds and new modified analogs.

We have previously reported oleylethanolamide analogs as PPARalpha activators [2] and cannabinoid antagonist derivatives containing a 1,2,4-triazole motif [3]. More recently we have described dual ligands integrating in one molecule the pharmacophore of the fibrates, fenofibrate (PPAR agonist) and a structural motif of rimonabant, a proven CB1 antagonist/inverse agonist using the strategy known as “designed multiple ligands” (DML) [4].

Purpose. Synthesis and evaluation of a new family of dual ligands resulting from merging into a single structure the well-known cannabinoid rimonabant with several alkylic scaffolds.

Methods.

Synthesis. The 1,5-diarylpyrazole derivatives were synthesized from ethyl 5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxylate following the procedure described in Pérez-Fernández *et al*.[5]

Pharmacological evaluation. The affinity of the new compounds was evaluated measuring their ability to displace [^{3}H]CP55940 from human cannabinoid CB_1 and CB_2 receptors transfected into HEK293 EBNA cells [5].

Luciferase reporter gene assays were performed following the procedure described in Cano *et al*.[2]

Results. In order to study structure activity relationships (SAR), a new series of 1,5-diarylpyrazole derivatives was synthesized. An example of this family is represented in Fig 1. They were tested at cannabinoid CB_1 and CB_2 receptors by radioligand binding assays and as PPAR by luciferase reporter gene assay. In binding assays they have shown values in the nanomolar range. Evaluation of the PPAR alpha activity has also been performed.

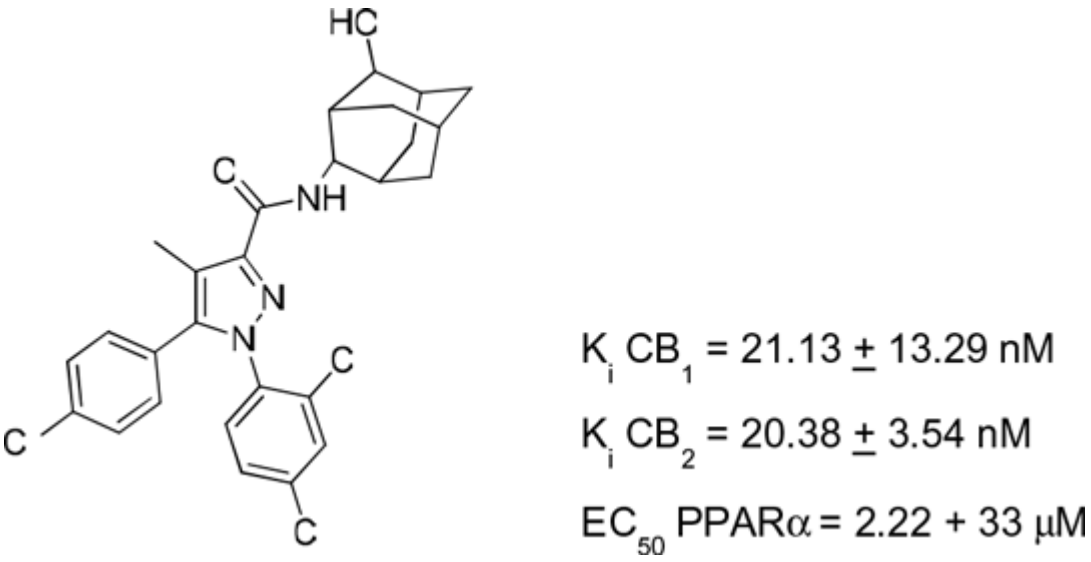

Figure 1. Dual CB and PPAR ligand.

Conclusion. This family of synthesized 1,5-diarylpyrazoles derivatives could be interesting leads in the search for a new class of dual ligands capable of modulating metabolism with potential neuroprotective activities.

References.

[1] Serrano A et al, Curr Obes Rep 1:216, 2012

[2] Cano C et al, J Med Chem 50:389, 2007

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[4] Pérez-Fernández R et al, ACS Med Chem Lett 2:793, 2011

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