Development of new bioactive 2-substituted benzopyrans: potential agents for treating metabolic syndrome

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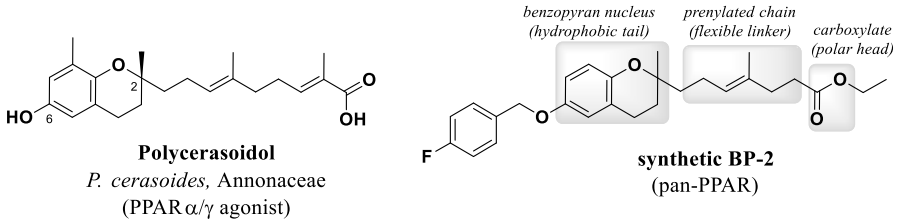
I will present the peroxisome proliferator-activated receptors (PPARs), their target role in treating metabolic syndrome and the impact of ligands that activate them [1]. I will talk mainly about a class of natural and synthetic compounds with significant biological activities: the 2-prenylated benzopyrans. In 1995, we isolated polycerasoidol from *Polyalthia cerasoides* (Annonaceae), and we have proved its potent dual PPARα/γ agonist activity and anti-inflammatory effect [2]. Next, I will focus on the synthesis, PPAR activity and structure-activity relationships (SAR) of 2-prenylated or 2-substituted benzopyrans and structural analogues [3-5]. I will explain the synthesis of 2-prenylated *O*-alkoxylated benzopyrans and the 2-alkyl hydrazone benzopyrans [3, 4], as well as the discovery of a lead compound, the BP-2, which improved metabolic alterations in a diabetic and obese mouse model [5]. The synthetic approaches involve key reactions such the condensation between an *o*-hydroxyacetophenone with an alkyl ketone via Aldol reaction and an *oxo*-Michael addition to build the chromanol nucleus, the Grignard reaction and Johnson-Claisen rearrangement to introduce the isoprenoid unit, and the Horner-Wadsworth-Emmons olefination to form the *O*-alkoxylated-α,β-unsaturated esters, among others. I will comment the synthesis and PPAR activity of 2-prenylated quinolines via Friedländler condensation, as potential bioisosters of 2-prenylated benzopyrans [6]. Therefore, the 2-prenyaletd and 2-substiyuted benzopyrans and quinoline analogues with dual or pan-PPAR agonism emerge as lead compounds useful for developing candidates to prevent cardiovascular diseases associate with metabolic disorders.



Polycerasoidol
P. cerasoides, Annonaceae
(PPAR α/γ agonist)

synthetic BP-2
(pan-PPAR)

References: [1] C. Villarroel-Vicente et al. *Eur. J. Med. Chem*. 2021, 221, 113535; [2] A. Bermejo et al. *J. Nat. Prod.* 2019, 82, 1802−1812; [3] A. García et al. *ACS Med. Chem. Lett.* 2021, 12, 1783-1786; [4] A. García et al. *Eur. J. Med. Chem.* 2024, 265, 116125; [5] P. Marques et al. *Pharmacol. Res*. 2023, 187, 106638; [6] C. Villarroel-Vicente et al. *Bioorg. Med. Chem. Lett.* 2024, 106, 129770.