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Design, synthesis and pharmacological profiling of dual modulators of soluble epoxide hydrolase and peroxisome proliferator activated rezeptors

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The basic idea of this study comprehends the development of polypharmacological agents for the treatment of the metabolic syndrome. Several dual modulators of the peroxisome proliferatior-activated receptors (PPARs) and the soluble epoxide hydrolase (sEH) have been rationally designed, synthesized and pharmacologically profiled. It was possible to generate a number of active compounds containing the common pharmacophores of both targets (sEH/PPAR). The potency of sEH inhibition, determined in an in vitro assay with recombinant enzyme, is located in a sub micromolar range. The ability of the PPAR activation was evaluated in a cell-based reporter-gene assay. At a micromolar concentration, relative activations could be demonstrated, ranging from full agonists to partial modulators. The compounds activated PPAR in a subtype-selective as well as in a nonselective way. The lead compound showed no cytotoxic effect up to 30 μM in HepG2 cells. Water solubility was observed up to 500 μM in PBS buffer at pH 7.4 with 5 % of DMSO. The initiation of adipocyte differentiation was shown in human adipocytes and murine fibroblasts. An *in vivo* exposure study in mice presented reasonable pharmacokinetic parameters. Future *in vivo* studies in diabetic mouse models will show the value of this approach for the therapy of metabolic syndrome-related diseases.

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