2-{3-[2-(4-CHOROPHENYL)ETHOXY]-PHENYLTHIO}-2-METHYLPROPANOIC ACID, A NEW FIBRATE-LIKE COMPOUND WITH ANTIDIABETIC AND HYPOLIPIDEMIC ACTIVITY

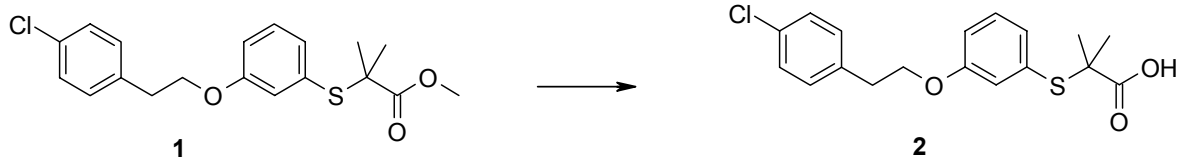
Natalina Dell'Uomo,[a] Emanuela Tassoni,[a] Tiziana Brunetti,[a] Pompeo Pessotto,[b] Ferdinando Maria Milazzo,[b] Anna Floriana Sciarroni,[b] Francesco De Angelis,[c] Alessandro Peschechera,[b] Maria Ornella Tinti,[a] Paolo Carminati,[d] Fabio Giannessi.[b]

[a]Dept. of Chemical Research, [b]Dept. of Endocrinology and Metabolism, [d]R&D Dept., Sigma-Tau, Via Pontina km 30.400, 00040 Pomezia (Rome), Italy
[c]Dept. of Chemistry, Chemical Engineering and Materials, University of L'Aquila, L'Aquila, Italy

We report the synthesis, *in vitro* characterization and *in vivo* activity as hypolipidemic and antidiabetic, of a new fibrate-like compound **(1)** and of its corresponding acid **(2)**.

In vitro transactivation tests for activity as PPAR ligands were performed on mouse receptors transfected into monkey kidney COS-7 cells (for PPARα), and into mouse embryo NIH-3T3 fibroblasts (for PPARγ). **1** proved a more potent PPARα activator with respect to reference marketed fibrates, fenofibrate and bezafibrate, resulting in a subtype-selective PPAR activator. We found that ester **1** was promptly converted into **2** *in serum* and *in vivo*, and the latter showed dual activation of PPARα and PPARγ. As PPARγ isoform is involved in the mediation of antihyperglycemic activity, the antidiabetic activity of **2**, and indirectly of **1**, might be explained, at least in part**,** in terms of PPARγ activation.

In *db/db* diabetic mice **2** was able to maintain the best glycemic control and insulin-sensitizing activity, based on glucose and insulin levels. HDL cholesterol levels were increased by treatment with both **1** and **2** but not with rosiglitazone, while triglyceride levels were lowered by all the compounds. The undesirable increment of body weight observed with rosiglitazone was not observed in animals treated with **2** or **1,** as with the reference fibrates. Compound **1** was evaluated also in other models of hyperlipidemias and PPARα activation: mice fed with a cholesterol-rich diet, and transgenic mice expressing human Apolipoprotein A-I.



1 **2**

The results obtained indicate **2** (ST2518) as a promising candidate for further investigation and preclinical development as insulin-sensitizing antidiabetic and hypolipidemic agent.