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2-{3-[2-(4-Chlorophenyl)ethoxy]-phenylthio}-2-methylpropanoic Acid: a Fibrate-Like Compound with Hypolipidemic and Antidiabetic Activity

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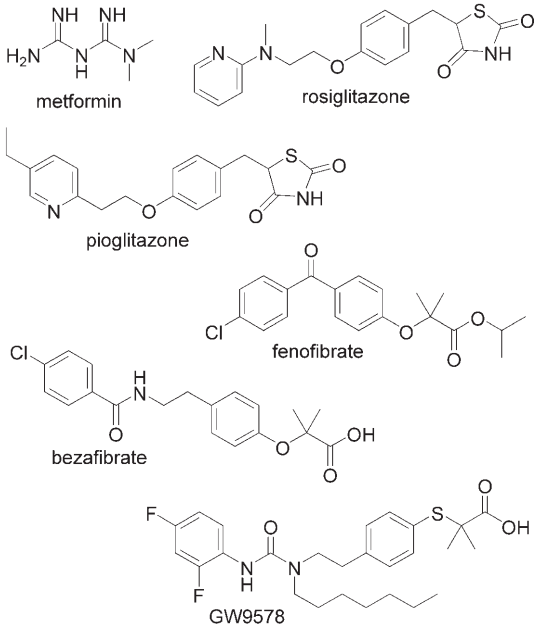

Diabetes is a complex metabolic disease which has reached epidemic proportions; its continuously increasing incidence is a consequence of the excessive caloric intake and lack of physical activity that characterize the western lifestyle. The progressive impairment of insulin sensitivity and eventual deterioration of β-cell function are the underlying causes of the overt disease.[1] The classical and commonly used treatments for lowering glycemia are the insulin secretagogues, such as the sulfonylureas, and metformin, an insulin sensitizer with a mechanism of action that is still under investigation.[2–4] In recent years rosiglitazone and pioglitazone have entered the market as insulin sensitizers and anti-hyperglycemic drugs. They are representatives of the new thiazolidinedione (TDZ) class of agents, which elicit their effects through activation of the γ isoform of the nuclear peroxisome proliferator-activated receptor (PPARγ).[5,6] The activity of TDZs in humans is accompanied by weight gain and risk of edema,[7,8] whereas the liver toxicity observed with troglitazone, the first marketed (and soon thereafter withdrawn) representative of this family, seems to be more the result of its particular chemical structure than of its TDZ class-related mechanism of action.[9] Despite an improvement in the ability to control glycemia, the prevention and management of the negative cardiovascular aspects of the disease remain the focus of open primary research, as such aspects rank diabetes the fourth leading cause of mortality in developed countries.[10] In this context, a drug that is able to effectively correct dyslipidemia as well as hyperglycemia and insulin sensitivity is certainly of great interest.

Fibrates such as fenofibrate and bezafibrate have been widely used for decades as hypolipidemic, antiatherosclerotic, and cardioprotective agents,[11,12] and are known to act through the activation of the α isoform of PPAR (PPARα).[13,14] For these reasons, compounds that activate both PPARα and PPARγ receptors (PPARα/γ mixed agonists) are considered to be very promising targets (ref. [15] and references therein), but only a few of them bear fibrate-related structures.[15d,e] In the last few years, new hypolipidemic PPARα agonists with improved potency and selectivity have also appeared, such as GW9578[16] and its closely related analogue GW7647,[17] both of which are characterized by a thioisobutyrate moiety.

During our search for new hypolipidemic and anti-hyperglycemic agents, we found quite unexpectedly that compound **3** (Scheme 1), which is structurally related to the fibrates, considerably improves diabetic conditions in C57BL/KsJ *db*/*db* diabetic mice (Table 1). In particular, the decrease in glucose level was similar to that effected by rosiglitazone, even if **3** was administered at a higher dose (25 instead of 5 mg kg^{-1}, twice a day by oral gavage for 25 days), with greatly improved homogeneity of values. This last point should not be underestimated, as in our experience, not all animals in experimental groups respond to rosiglitazone and similar compounds. The same has also been reported in studies with humans.[18] In an oral glucose tolerance test (OGTT) after 19 days of treatment, the glycemic area under curve (AUC) was considerably lower in the case of **3** with respect to control and fibrate results, and

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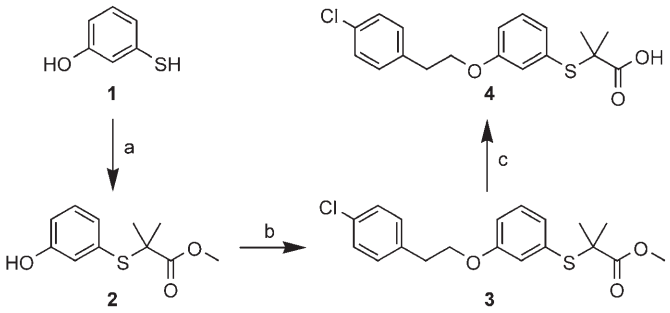
Table 1. Effects of fibrate analogue **3** on plasma parameters in mice.[a]

Compound	Dose [mg kg^{-1}]	Body weight [g]	GLU [mg dL^{-1}][b]	TG [mg dL^{-1}][c]	INS [ng mL^{-1}][d]	AUC [mg dL^{-1} min^{-1}][e]	HDLC [mg dL^{-1}][f]
Control		28.3 ± 0.8	456 ± 45	95 ± 7	6.5 ± 0.7	50057 ± 3085	82 ± 6
3	25.0	35.9 ± 0.6[g]	206 ± 8[g]	45 ± 3[g]	1.4 ± 0.1[g]	24527 ± 889[g]	98 ± 3[h]
fenofibrate	24.7[i]	34.5 ± 1.0[j]	553 ± 30	67 ± 3[j]	3.6 ± 0.1[j]	45192 ± 1546	96 ± 4
bezafibrate	24.8[i]	35.2 ± 1.3[j]	537 ± 22	88 ± 13	3.7 ± 0.3[j]	44476 ± 1827	94 ± 4
rosiglitazone	5.0	42.1 ± 2.5[g]	296 ± 39[h]	44 ± 4[g]	2.3 ± 0.2[g]	38174 ± 3555[h]	65 ± 4[h]

[a] Data are mean ± SEM for six mice per compound group, and were determined from *db*/*db* male mice in post-absorptive state after 25 days of treatment with compounds administered by oral gavage twice daily; for AUC: data gathered from mice fasted overnight after 19 days of treatment. [b] Plasma glucose. [c] Plasma triglycerides. [d] Plasma insulin. [e] AUC for glucose from OGTT. [f] Plasma HDL cholesterol. [g] Significant difference from control group at $p < 0.001$ (Student *t* test). [h] Significant difference from control group at $p < 0.05$ (Student *t* test). [i] Dose equimolar to **3** at 25 mg kg^{-1}. [j] Significant difference from control group at $p < 0.01$ (Student *t* test).



Scheme 1. a) NaH (1.2 equiv), methyl(2-bromo-2-methyl)propanoate (1 equiv), CH_3CN (anhyd), 0 °C 1 h then RT 18 h, 81%; b) 4-chlorophenethyl alcohol (1 equiv), DIAD (1.3 equiv), triphenylphosphine (1.3 equiv), THF (anhyd), 18 h, 71%; c) MeOH/NaOH (9:4, 1 N), 48 h, 88%. DIAD = diisopropyl azodicarboxylate.

even with respect to those of rosiglitazone-treated animals. The lipid profile improvement was evidenced by a decrease in triglycerides and by an increase in HDL cholesterol.

The in vivo hypolipidemic fibrate-like profile of **3** was confirmed in two different models: mice fed a cholesterol-rich diet[19,20] and transgenic mice expressing human apolipoprotein A-I (hApoAI), which is under control of PPARα and PPARβ/δ.[21,22] The latter is a more recently investigated and ubiquitous isoform, the beneficial activation effects of which, in terms of lipid profile, appear to partially overlap those of the α isoform.[22] In the first model, compound **3** was observed to decrease serum and liver total cholesterol and to increase hepatic peroxisomal acyl-CoA oxidase (ACO) activity (Table 2), whereas in transgenic mice it was observed to increase the levels of plasma HDL cholesterol and hepatic ACO activity and to decrease triglyceride levels (Table 3). Similar results in both experiments were obtained with fenofibrate used as reference compound, but not with the PPARγ agonist rosiglitazone, as expected.

Evaluating the conversion of ester **3** into its acidic form **4**, we found that only **4** was detected by HPLC–MS analysis in sera in vitro from *db*/*db* mice after 15 min and in vivo after 1 hour following oral administration.

As **3** and its acid **4** emerged as promising candidates for the investigations reported herein, we appreciated their easy availability from a synthetic point of view in the course of several preparations (on a scale of from one gram to several hundred grams). They were prepared by starting with the sodium salt of 3-hydroxythiophenol **1** in reaction with methyl(2-bromo-2-methyl)propanoate to give **2** in 81% yield, followed by Mitsu-

Table 2. Effects of fibrate analogue **3** on total cholesterol levels and ACO activity.[a]

Compound	Dose [mg kg^{-1}]	TPC [mg dL^{-1}][b]	TLC [%][c]	ACO [nmol mg$_{protein}^{-1}$ min^{-1}][d]
Control		348 ± 40	3.3 ± 0.3	70 ± 11
3	25.0	261 ± 27	1.8 ± 0.3[e]	371 ± 23[f]
fenofibrate	24.7[g]	260 ± 20	2.6 ± 0.3	285 ± 41[e]
rosiglitazone	5.0	361 ± 29	3.7 ± 0.1	98 ± 13

[a] Data gathered from male mice in post-absorptive state after having been fed a cholesterol-rich diet for 39 days; compounds were administered by oral gavage twice daily over the final 18 days of the course; data are mean ± SEM for six mice per group. [b] Total plasma cholesterol. [c] Total liver cholesterol. [d] Liver peroxisomal acyl-CoA oxidase activity. [e] Significant difference from control group at $p < 0.01$ (Student *t* test). [f] Significant difference from control group at $p < 0.001$ (Student *t* test). [g] Dose equimolar to **3** at 25 mg kg^{-1}.

Table 3. Effects of fibrate analogue **3** on HDL cholesterol and ACO activity.[a]

Compound	Dose [mg kg^{-1}]	HDLC [mg dL^{-1}][b]	ACO [nmol mg$_{protein}^{-1}$ min^{-1}][c]	TG [mg dL^{-1}][d]
Control		148 ± 7	80 ± 8	64 ± 4
3	25.0	186 ± 4[e]	453 ± 31[f]	45 ± 3[e]
fenofibrate	24.7[g]	209 ± 18[e]	424 ± 25[f]	58 ± 4
rosiglitazone	5.0	152 ± 8	153 ± 15[e]	65 ± 6

[a] Data gathered from hApoAI transgenic mice in post-absorptive state after 15 days of treatment (oral gavage, twice daily); data are mean ± SEM for five mice per group. [b] Plasma HDL cholesterol. [c] Liver peroxisomal acyl-CoA oxidase activity. [d] Plasma triglycerides. [e] Significant difference from control group at $p < 0.01$ (Student *t* test). [f] Significant difference from control group at $p < 0.001$ (Student *t* test). [g] Dose equimolar to **3** at 25 mg kg^{-1}.

Table 4. Effects of fibrate analogues **3** and **4** on plasma parameters in mice.[a]

Compound	Dose [mg kg^{-1}]	Body weight [g]	GLU [mg dL^{-1}][b]	INS [ng mL^{-1}][c]	AUC [mg dL^{-1} min^{-1}][d]	HDLC [mg dL^{-1}][e]	TG [mg dL^{-1}][f]
Control		36.5 ± 1.4	560 ± 26	12.1 ± 1.5	43438 ± 2485	78 ± 4	91 ± 5
3	12.5	38.4 ± 0.9	404 ± 55[g]	11.0 ± 2.7	25038 ± 2529[h]	131 ± 5[h]	46 ± 2[h]
4	12.0[j]	37.2 ± 2.5	238 ± 25[h]	3.4 ± 0.5[h]	27939 ± 1999[h]	114 ± 4[h]	41 ± 2[h]
rosiglitazone	5.0	40.4 ± 0.5	281 ± 42[h]	7.0 ± 0.9[g]	25135 ± 3477[i]	88 ± 3	58 ± 5[h]

[a] Data are mean ± SEM for six mice per compound group, and were determined from *db*/*db* male mice in post-absorptive state after 13 days of treatment with compounds administered by oral gavage twice daily; for AUC: data gathered from mice fasted overnight after 11 days of treatment. [b] Plasma glucose. [c] Plasma insulin. [d] AUC for glucose from OGTT. [e] Plasma HDL cholesterol. [f] Plasma triglycerides. [g] Significant difference from control group at $p < 0.05$ (Student *t* test). [h] Significant difference from control group at $p < 0.001$ (Student *t* test). [i] Significant difference from control group at $p < 0.01$ (Student *t* test). [j] Dose equimolar to **3** at 12.5 mg kg^{-1}.

nobu reaction with 4-chlorophenethyl alcohol to give **3** in 71% yield. The acid **4** was prepared in 88% yield by hydrolysis of the corresponding ester. Alternatively, **3** could be prepared from the phenolate anion of **2** through nucleophilic substitution on the methanesulfonyl derivative of 4-chlorophenethyl alcohol, which is easily obtained by reaction with methanesulfonyl chloride.

The main structural differences between the classical fibrates and compounds **3** and **4** are in the replacement of the ether group by a thioether function and in the *meta*, rather than the classical *para*, substitution pattern of the phenolic moieties (see the fenofibrate structure above). With regard to the latter point, the *para* isomer of **3** was completely inactive toward the control of glycemia under identical experimental conditions (data not shown).

For a direct comparison between **3** and **4** as antidiabetic agents, they were tested in *db*/*db* mice at a lower dose (12.5 mg kg^{-1}). Only **4** was observed to maintain the best glycemic control and insulin-sensitizing activity, based on glucose and insulin levels (Table 4). HDL cholesterol levels, which are increased in the presence of fibrates, were also increased by treatment with **3** and **4** but not with rosiglitazone, whereas triglyceride levels were lowered by all the compounds. Considering the facile transformation of **3** into **4** discussed above, the slight difference between the in vivo profiles of the ester and the acid can be tentatively associated with the difference between their in vitro profiles (see below), and to differences in pharmacokinetics. Notably, another advantage of **3** and **4** over rosiglitazone is that they do not cause a marked increase in body weight, as is the case with the reference fibrates (Tables 1 and 4). Increased body weight is particularly dangerous for sufferers of diabetes and hyperlipidemia, as most subjects are already obese or overweight, conditions linked to insulin resistance.

Compound **4** was also evaluated in mice fed a cholesterol-rich diet and in hApoAI transgenic mice, with fenofibrate and rosiglitazone as reference compounds. Indeed, **4** gave a good profile as hypolipidemic agent (Tables 5 and 6).

Table 5. Effects of fibrate analogue **4** on total cholesterol levels and ACO activity.[a]

Compound	Dose [mg kg^{-1}]	TPC [mg dL^{-1}][b]	TLC [%][c]	ACO [nmol mg$_{protein}^{-1}$ min^{-1}][d]
Control		350 ± 27	5.7 ± 1.2	102 ± 8
4	25.0	200 ± 29[e]	3.5 ± 0.6	494 ± 39[f]
fenofibrate	25.7[g]	308 ± 18	5.3 ± 0.6	346 ± 39[f]
rosiglitazone	5.0	354 ± 23	5.5 ± 0.9	220 ± 23[e]

[a] Data gathered from male mice in post-absorptive state after having been fed a cholesterol-rich diet for 45 days; compounds were administered by oral gavage twice daily over the final 18 days of the course; data are mean ± SEM for six mice per group. [b] Total plasma cholesterol. [c] Total liver cholesterol. [d] Liver peroxisomal acyl-CoA oxidase activity. [e] Significant difference from control group at $p < 0.01$ (Student *t* test). [f] Significant difference from control group at $p < 0.001$ (Student *t* test). [g] Dose equimolar to **4** at 25 mg kg^{-1}.

Table 6. Effects of fibrate analogue **4** on HDL cholesterol and ACO activity.[a]

Compound	Dose [mg kg^{-1}]	HDLC [mg dL^{-1}][b]	ACO [nmol mg$_{protein}^{-1}$ min^{-1}][c]	TG [mg dL^{-1}][d]
Control		163 ± 6	89 ± 7	75 ± 6
4	25.0	252 ± 18[e]	506 ± 14[f]	36 ± 3[f]
fenofibrate	25.7[g]	220 ± 19[h]	397 ± 14[f]	78 ± 6
rosiglitazone	5.0	144 ± 18	108 ± 7	74 ± 10

[a] Data gathered from hApoAI transgenic mice in post-absorptive state after 15 days of treatment (oral gavage, twice daily); data are mean ± SEM for five mice per group. [b] Plasma HDL cholesterol. [c] Liver peroxisomal acyl-CoA oxidase activity. [d] Plasma triglycerides. [e] Significant difference from control group at $p < 0.01$ (Student *t* test). [f] Significant difference from control group at $p < 0.001$ (Student *t* test). [g] Dose equimolar to **4** at 25 mg kg^{-1}. [h] Significant difference from control group at $p < 0.02$ (Student *t* test).

Compounds **3** and **4** were also evaluated for their in vitro transactivation activity toward mouse and human PPARα and PPARγ transfected into COS-7 and NIH-3T3 cells. As shown in Table 7, compound **3** proved to be a subtype-selective PPARα activator; it is unable to activate the PPARγ receptor, which is the isoform widely recognized as a mediator of anti-hyperglycemic activity. Moreover, **3** proved to be an effective mouse

Table 7. *In vitro* PPAR transactivation activities of fibrate analogues **3** and **4**.[a]

	mPPARα[b]		mPPARγ[c]		hPPARα[b]		hPPARγ[b]	
Compound	EC_{50} [μM]	Efficacy[d]	EC_{50} [μM]	Efficacy[d]	EC_{50} [μM]	Efficacy[d]	EC_{50} [μM]	Efficacy[d]
3	15.8	700	NA[e]	NA[e]	1.2	165.2	NA[e]	NA[e]
4	5.63	770	9.0	31.8	0.223	153.0	76.44	86.3
fenofibrate	13.45	100	NA[e]	NA[e]	31.34	100	63.5	42.7
rosiglitazone	NA[e]	NA[e]	11.62	100	NA[e]	NA[e]	1.4	100

[a] Cells were incubated for 24 or 48 h before chloramphenicol acetyltransferase (CAT) activity measurement; data were obtained from at least two independent experiments performed in duplicate. [b] Transactivation determined in COS-7 cells transiently transfected with pSG5-mPPARα/GAL4, pFA-hPPARα/GAL4 or pFA-hPPARγ/GAL4 expression vectors, and in each case both pUAS(5X)-E1b-CAT and pSV-lacZ. [c] Transactivation measured in NIH-3T3 cells transiently transfected with the pSG5-mPPARγ expression vector, and both pBLCAT2-PPRE and pSV-lacZ. [d] Maximum efficacy reported as percentage of the maximum efficacy of reference compounds (fenofibrate for PPARα; rosiglitazone for PPARγ). [e] Not active at the concentrations tested.

PPARα activator (EC_{50} = 15.8 μM) with an efficacy sevenfold greater than the marketed reference compound fenofibrate. It is also active in very low doses, at which reference fibrates are completely inactive (data not shown). The acid **4**, however, showed dual activation of mouse PPARα (EC_{50} = 5.63 μM: eightfold greater efficacy than that of fenofibrate) and PPARγ (EC_{50} = 9.0 μM: efficacy 31.8% that of rosiglitazone). Therefore, the anti-hyperglycemic activity of **4** (and indirectly of **3**) can be explained, at least in part, through activation of PPARγ.

The transactivation activity of **4** toward the human PPARs is even more pronounced for the α isoform (EC_{50} = 0.223 μM) with efficacy ≈25-fold higher than that of fenofibrate at lower doses (data not shown). However, the activation of human PPARγ appeared to be blunted (EC_{50} = 76.44 μM), although the activation with **4** administered at higher doses was similar to the maximal activation observed with rosiglitazone.

It is difficult to foresee the exact impact these findings will have in the clinical setting, but in our opinion, it is reasonable to predict a good profile for compound **4** as a fibrate with strong anti-hyperlipidemic activity and with antidiabetic activity that can be optimized through dose calibration. The complete characterization of compounds **3** and **4** as PPAR agonists (in terms of the mouse and human PPARβ/δ isoforms) is also part of our future research direction.

In conclusion, the new fibrate-like compound **4** holds potential for the treatment and prevention of life-threatening cardiovascular complications typically associated with hyperlipidemia and diabetes, and for the control of glycemia through enhancement of insulin sensitivity. These effects may be free from at least some of the unwanted side effects characteristic of pure PPARγ agonists. Therefore, **4** (ST2518) has been selected for further investigations and preclinical development. An evaluation of its pharmacological properties in further mouse or rat models of diabetes, insulin-resistance, and dyslipidemia is part of our programmed research activities.

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