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ω-Substituted alkyl carboxylic acids as antidiabetic and lipid-lowering agents

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Abstract – In screening experiments certain ω-substituted alkyl carboxylic acids were found to produce an increase in insulin-stimulated ^{14}C-acetate incorporation into triglycerides, which may indicate an improvement in the action of insulin. Antidiabetic and lipid-lowering properties in genetically diabetic ob/ob mice demonstrated the in vivo relevance of the insulin-potentiating effects seen in vitro. The chemical structures of the ω-substituted alkyl carboxylic acids with insulin-potentiating effects correspond to the general formula ring–spacer–COOH. A close structure–activity relationship was observed. The most potent compound in ob/ob mice was **3e**, which normalized blood glucose as well as hyperinsulinaemia and lowered serum triglycerides and cholesterol by 52% and 37%, respectively. On the basis of these results, ω-substituted alkyl carboxylic acids are interesting as a new class of oral anticiabetic agents with insulin-sensitizing and lipid-lowering activity. © Elsevier, Paris

ω-substituted alkyl carboxylic acids / insulin sensitizer / lipid lowering

1. Introduction

Non-insulin-dependent diabetes mellitus (NIDDM) is characterized by a high level of blood glucose, abnormalities of insulin secretion and by insulin resistance of the peripheral tissues [1]. Insulin resistance plays a key role in the pathogenesis of type II diabetes and is often associated with a variety of other disorders like obesity, dyslipidaemia (hypertriglyceridaemia and low levels of high-density lipoprotein (HDL) cholesterol) and hypertension [2, 3]. This constellation of disturbances is summarized under the name metabolic syndrome, and is associated with a high risk for development of late diabetic complications, e.g. coronary artery disease [4] and nephropathy [5]. The pathogenetic mechanism of NIDDM is not fully understood.

New oral antidiabetic agents have been developed – the so-called insulin sensitizers [6]. Their mode of action is different from that of established antidiabetics like sulfonylureas [7] and biguanides [8]. Ciglitazone [9] was the first compound in this new class of thiazolidinediones. Since the discovery of Ciglitazone a number of other thiazolidinediones, e.g. Pioglitazone [10] and Englitazone [11], have been synthesized. Their antidiabetic action is reported to be characterized by amelioration of hyperglycaemia and hyperinsulinaemia [12, 13] and indicates an improvement in insulin resistance.

Activation of PPARγ-receptors and modulation of protein synthesis relevant for glucose metabolism may at least explain in part the antidiabetic mode of action at the molecular level [14, 15]. Induction of adipogenesis causing increased weight gain is described as consequence of PPARγ activation by thiazolidinediones [16, 17].

Troglitazone (5-[4-(6-hydroxy-2,5,7,8-tetramethylchroman-2-yl-methoxy)benzyl]-2,4-thiazolidinedione) is the first thiazolidinedione available for therapeutic use in NIDDM. The most important features of Troglitazone are reductions in plasma glucose and insulin levels and a decrease in insulin resistance [18]. The relevance of this pharmacological approach in the therapy of NIDDM has been demonstrated in clinical trials [19–22].

Antidiabetic effects like amelioration of hyperglycaemia, hyperinsulinaemia and reduction of glycated haemo-

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globin were only observed in some NIDDM patients ('responders') in a relatively high dose range of Troglitazone. Lowering of blood lipids also contributes to improvement of disturbed metabolic situation in NIDDM patients. The mode of action at the molecular level is not fully understood.

Our aim was to search for compounds with insulin-potentiating properties. Because of the high daily dosage of Troglitazone the compounds sought were required to be more potent. Additionally, structurally new compounds can be expected to have a different toxicological profile from that of the thiazolidinediones and this offers further advantages.

In this paper we present the synthesis, analytical and pharmacological characterization of ω-substituted alkyl carboxylic acids with insulin-sensitizing potency and lipid-lowering activity in vitro and in vivo.

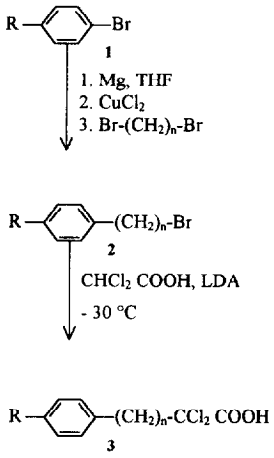
2. Chemistry

The 2,2-dichloroalkane carboxylic acids (**3**, **4**, **5**, **6**, **10**, **13**, **16**, **18**, **20**, **24**) were prepared in a straightforward manner by alkylation of the dianion of dichloroacetic acid with alkylhalides, mainly alkylbromides. The reaction is best performed at –30 °C in dimethoxyethane or tetrahydrofurane. Lower temperatures slow down the alkylation step too much, whereas higher temperatures lead to self-condensation products of dichloroacetic acid due to the limited stability of the corresponding dianion.

The required alkylbromides were obtained directly from α,ω-dibromoalkanes in different ways. In case of the arylalkyl or cycloalkyl alkylbromides the Tsuji–Schlosser coupling [23–25] provides the most efficient method (*figure 1*).

Phenoxyalkylbromides (**9a–e**) are easily synthesized by alkylation of the corresponding phenolates (*figure 2*). This method can also be used for the preparation of phenylthioalkylbromides from their thiolates (not shown). The same procedure was used for compounds containing oxygen or sulphur in the middle of the alkyl chain (**13**), in the latter case reaction between thiolate and a ω-bromo-2,2-dichlorocarboxylic acid ester (**14**) was equally efficient (*figure 3*).

Unsaturated alkylbromides e.g. **23** were obtained by Wittig reaction of benzaldehydes and appropriate bromoalkyl phosphonium salts. Compound **24** was prepared by reaction of **23** with dichloroacetic acid. Careful catalytic hydrogenation gave the saturated dichlorocarboxylic acid (**3b**) (*figure 4*) without loss of chlorine. For some rare oddly numbered dibromoalkanes this represents an alternative route to the procedure shown in *figure 4*.



1/2/3	R	n
a	H-	8
b	H-	10
c	H-	12
d	Cl-	5
e	Cl-	10
f	CH_3S-	10
g	$(CH_3)_3C$-	10

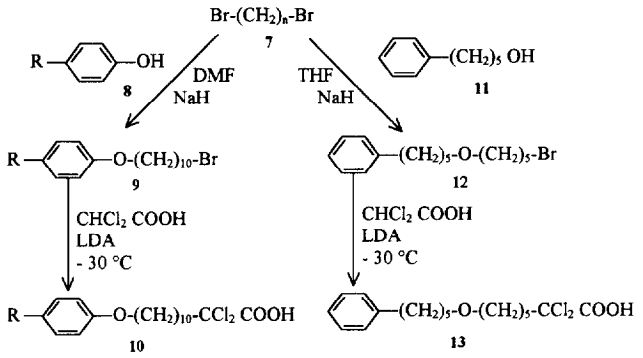
Figure 1. Synthesis of 2,2-dichlorocarboxylic acids by Tsuji–Schlosser coupling.

Table I shows formulas, yields and melting points of the new 2,2-dichlorocarboxylic acids.

3. Pharmacology

Enhancement of synthesis of fatty acids is one of the insulin-mediated changes of cellular metabolism [26]. The incorporation of radio-labelled precursors to investigate metabolism by various types of cells [27, 28] is a frequently used method. Effects of drugs on insulin-stimulated ^{14}C-acetate incorporation into triglycerides and cholesterol were therefore investigated in primary rat hepatocyte monolayer cultures [29]. Percent change to solvent (DMSO) treated controls is given.

Diabetic ob/ob mice, a commonly used animal model of NIDDM [30], were used to assess effects on glucose, insulin and lipids in blood. The data are given as percentage changes to the actual vehicle-treated control



9/10	R
a	H-
b	CH_3-
c	Cl-
d	$(CH_3)_3C$-
e	CH_3O-

Figure 2. Synthesis of 2,2-dichlorocarboxylic acids from phenoxyalkylbromides.

and as absolute values. Lowering of blood glucose to normoglycaemia (120 mg/100 mL) is rated as 100%.

4. Results and discussion

The effects of the ω-substituted alkyl carboxylic acid **3c,** the thiazolidinediones Pioglitazone and Troglitazone as well as the dioic acid BM 17.0249; 2,2,13,13-tetrachloro-tetra-1,14-dioic acid [$HOOCCCl_2(CH_2)_{10}CCl_2COOH$] on ^{14}C-triglyceride de novo synthesis in rat hepatocyte cultures are depicted in *figure 5*. The insulin-potentiating agents Pioglitazone and Troglitazone enhanced triglyceride synthesis as expected. The clearly higher triglyceride synthesis rate in the presence of **3c** may indicate an increase in insulin action for this drug too. The inhibition of triglyceride synthesis by the dioic acid, which belongs to compounds described as inhibitors of lipogenesis [31], demonstrates the sensitivity of the test system in both directions.

All ω-substituted alkyl carboxylic acids tested correspond to the general formula ring–spacer–carboxylic acid. They vary in the sort of ring and its substituents, the length of the spacer with and without hetero atoms or a double bond. A dichloromethylene group in the α-position to the carboxylic group to prevent metabolism by β-oxidation is constant in all these compounds. The effect on the incorporation rate of ^{14}C-acetate into triglycerides as well as cholesterol was investigated. More detailed information is given in *table II*.

Triglyceride de novo synthesis was enhanced as well as reduced, whereas cholesterol de novo synthesis was significantly reduced by most of the compounds tested. Thiazolidinediones enhanced triglyceride de novo synthesis but cholesterol de novo synthesis was unaffected or slightly increased. This observation may indicate an

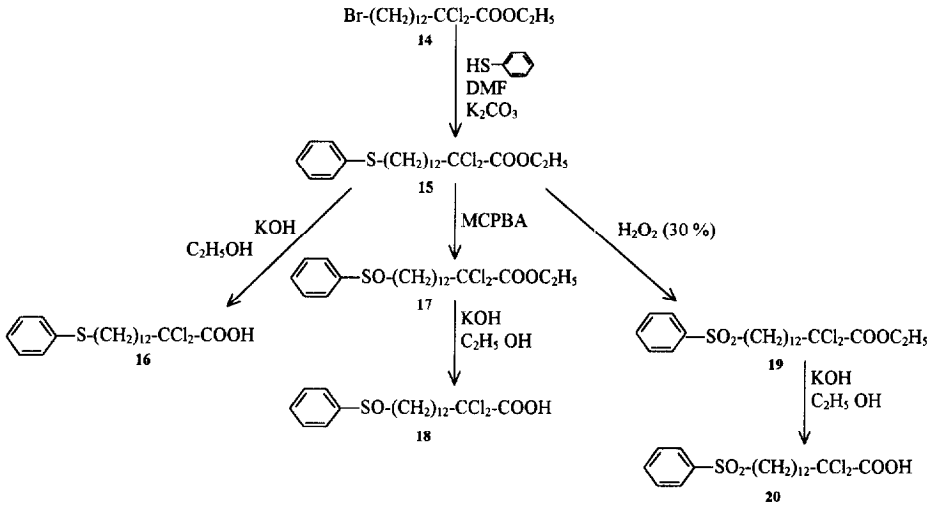


Figure 3. Synthesis of sulphur-containing 2,2-dichlorocarboxylic acids.

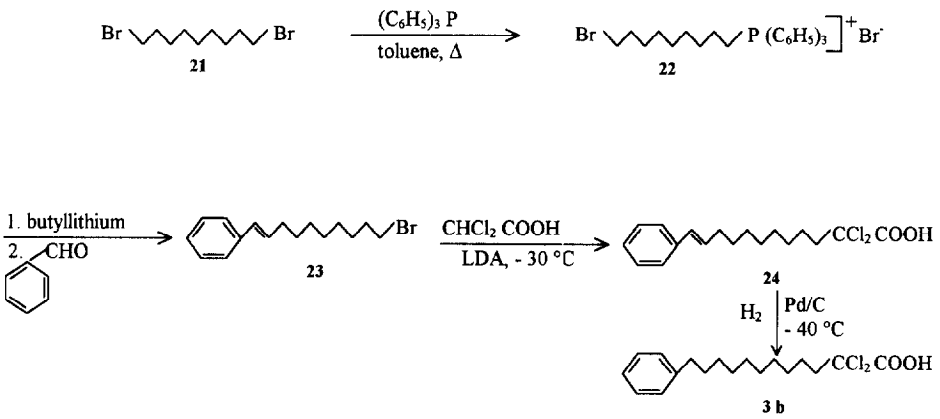


Figure 4. Synthesis of 2,2-dichloro-12-phenyl-11-dodecenoic acid and 2,2-dichloro-12-phenyl-dodecanoic acid.

overlapping of two effects for ω-substituted carboxylic acids, namely an increase in insulin-stimulated triglyceride synthesis and inhibition of lipogenesis.

A dramatic lowering of the incorporation rate into both triglycerides and cholesterol was found only with a carboxyl (**4**) or methyl group (**10b**) as substituents on the aromatic ring. It could be speculated that the methyl group of **10b** is oxidized by hepatocytes and that the metabolite of **10b** with a carboxylic group on the aromatic ring is really the active compound in the test system. Reduction of lipogenesis by inhibition of acetyl-CoA carboxylase is described for dioic acids [31] and may explain the effects observed for **4** and **10b**.

Furthermore, the inhibition of lipogenesis supports the proposed overlapping with insulin-stimulated triglyceride synthesis and suggests the need for the monocarboxylic structure for improvement of insulin action by this class of compounds.

Improvement of insulin action and reduction of lipogenesis suggest that amelioration of the diabetic status and lipaemia might be expected. The drugs were administered to diabetic ob/ob mice. Blood glucose as well as insulin, triglycerides and non-esterified fatty acids (NEFA) in serum were determined after an administration period of 5 days (*table III*).

A dramatic lowering of hyperglycaemia was found and even normoglycaemia was reached with some compounds. The extent of the reduction in blood glucose was mostly paralleled by a comparable amelioration of hyperinsulinaemia. Triglycerides and NEFA were generally reduced. The changes in the two parameters were not parallel and did not correlate to the lowering of blood glucose and insulin. This may be evidence that lipid lowering is not mediated by antidiabetic potency, but has a different mode of action. Furthermore, these in vivo findings support the conclusion drawn from the results of the in vitro experiments with an increase in insulin sensitivity and inhibition of lipogenesis.

Assessment of the chemical structure and the in vivo and in vitro activity shows a close relationship. Compounds with a phenyl group at the ω-end show an increase of amelioration of diabetic status with increasing numbers of methylene groups (**3a–c**). Substituents with properties as electron donators in the para position on the aromatic ring showed a further amelioration predominantly reduction of hyperinsulinaemia (**3d–g**). The strongest overall effects in vitro and predominantly in vivo were found using **3e**. A bulky substituent like *tert*-butyl (**3g**) did not produce better antidiabetic effects than electronegative substituents.

Carboxylic or methyl groups in the para position led to a clear reduction of hyperglycaemia, whereas hyperinsulinaemia was reduced only slightly in comparison to these effects. The concomitant reduction of blood lipids may suggest that the antidiabetic effect is mediated by reduction of lipogenesis as shown in hepatocytes, and not by an improvement in the action of insulin.

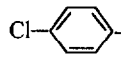
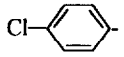
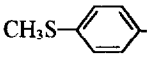
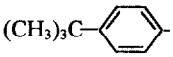
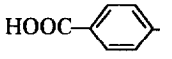
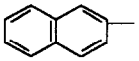
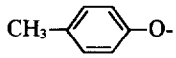
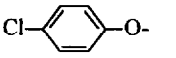
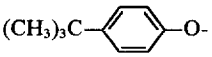
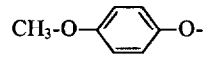
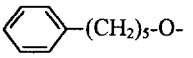
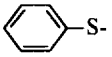
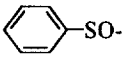
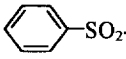
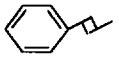
Replacement of the phenyl ring (**3b**) by naphthyl (**5**) or cyclohexyl (**6**) resulted in a higher in vivo potency but did not in excess of that of **3e**. Insertion of oxygen adjacent to the aromatic ring (**10a**) or in the middle of the methylene spacer (**13**) improved the antihyperglycaemic and antihyperinsulinaemic effect compared to **3b**.

Additional substitution in the para position (**10c–e**) enhanced both antidiabetic and lipid-lowering potency only in case of chlorine (**10c**), but the effects of **3e** were not exceeded.

Insertion of sulphur next to the aromatic ring, resulting in **16**, did not exceed the overall antidiabetic effects of **3e** and there were no effects on blood lipids. Oxidation of

Table I. Formulas, yields and melting points of the ω-substituted alkyl carboxylic acids.

$$R\text{-}(CH_2)_n\text{-}CCL_2COOH$$

Compound			Yield (%)	M.p. (°C)	
Number	*n*	R		Free acid	Sodium salt
3a	8		35	–	154–156
3b	10		94	–	157–159
3c	12		56	–	171
3d	5		74	–	158–162
3e	10		30	–	> 250
3f	10		14	–	143
3g	10		22 [a]	46–48	> 176
4	10		95	122–128	–
5	10		79	66–67	–
6	10		46	67–68	–
10a	10		63	58–60	–
10b	10		22	67–68	–
10c	10		50	63–64	–
10d	10		35 [a]	56–57	> 178
10e	10		20	68–69	–
13	5		43	83–84	–
16	12		92	74	–
18	12		95	68	–
20	12		97	69–71	–
24	8		45	50–52	–

[a] The yield is given for the free acid.

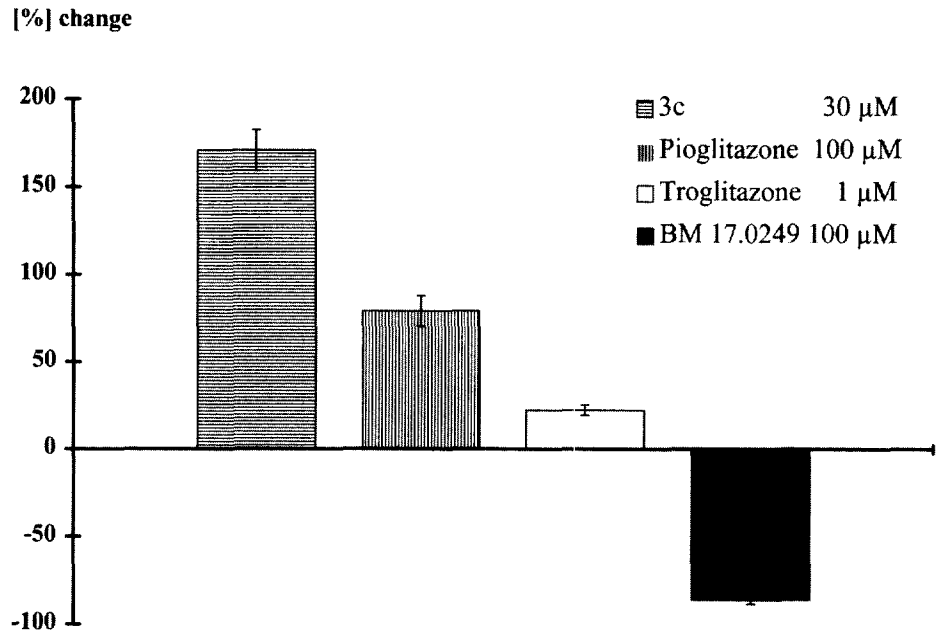


Figure 5. ^{14}C-acetate incorporation into triglycerides: effects of metabolically active compounds on ^{14}C-acetate incorporation into triglycerides in primary rat liver cell monolayer cultures. Data are given in % change of solvent-treated (DMSO: 0.1% final concentration) controls ($\bar{x} \pm$ SEM, $n = 4$–6 culture dishes from 2–3 preparations).

the sulphur to sulphoxide (**18**) and sulphone (**20**) improved the antidiabetic and triglyceride-lowering effect without any action on NEFA.

A double bond conjugated to the aromatic ring (**24**) resulted in a weak lowering of hyperinsulinaemia and even enhancement of free fatty acids in blood.

5. Conclusion

Insulin resistance is a primary feature of NIDDM and often associated with obesity and dyslipidaemia. This insulin-resistant state of the peripheral and hepatic tissue causes hyperinsulinaemia and impaired glucose utilization leading to overt diabetes. Therefore, amelioration of insulin resistance with a drug that also has a positive effect on lipid metabolism would provide a novel and useful means of treating NIDDM.

ω-Substituted alkyl carboxylic acids showed enhancement of insulin stimulated triglyceride de novo synthesis in rat hepatocytes. In contrast to thiazolidinediones, reduction of cholesterol de novo synthesis was also observed. Improvements in diabetic status and dyslipidaemia were shown in ob/ob mice.

The strongest activity in both test systems was observed for compounds with a minimum of 10 methylene groups in the spacer and a phenyl group with an electronegative substituent like chloro or methylsulphenyl in the para position.

All in all, the ω-substituted alkyl carboxylic acids are a structurally new class of insulin sensitizers with intense antihyperglycaemic and antihyperinsulinaemic potency in an animal model of NIDDM. Lipid-lowering is a further property. Because of their antidiabetic and lipid-lowering potency the substances may be of great interest in combatting the metabolic syndrome.

6. Experimental protocols

6.1 Synthesis

All ω-substituted alkyl carboxylic acids and their sodium salts were synthesized in the Department of Chemistry at Boehringer Mannheim. NMR spectra were performed on a Bruker AC-250 (^{1}H: 250 MHz, ^{13}C: 63 MHz). $CDCl_3$ was used as solvent for the free acids, DMSO-d_6 for their sodium salts. TMS served as reference substance; δ: 0 ppm. Melting points were determined using a Buechi melting point apparatus. Purification was carried out by flash chromatography or filtration at silica gel (Merck, Darmstadt).

6.1.1. 2,2-Dichloro-10-phenyldecanoic acid ***3a***

10 mL (1 mmol) of an orange–red solution of Li_2CuCl_4(prepared from $CuCl_2$ (1.344 g, 10.0 mmol), anhydrous LiCl (0.848 g,

Table II. Effects on lipid synthesis in hepatocytes. [a]

Compound	^{14}C-acetate-incorporation into	
	Triglycerides % change	Cholesterol % change
3a	−41 ± 7.3	−40 ± 3.0
3b	−3 ± 3.4	−11 ± 7.5
3c	36 ± 4.1	−13 ± 5.1
3d	8 ± 4.5	−20 ± 2.5
3e	−1 ± 6.9	−32 ± 3.4
3f	51 ± 11.3	−16 ± 7.4
3g	18 ± 7.2	−5 ± 2.6
4	−55 ± 3.4	−29 ± 2.6
5	−5 ± 5.9	−28 ± 2.1
6	−25 ± 4.9	−40 ± 4.1
10a	31 ± 15.1	−11 ± 2.0
10b	−60 ± 1.5	−27 ± 3.0
10c	28 ± 2.5	−36 ± 3.5
10d	28 ± 6.1	−16 ± 2.8
10e	13 ± 7.1	−6 ± 8.1
13	−16 ± 5.9	−10 ± 1.4
16	19 ± 4.4	−21 ± 2.3
18	32 ± 9.7	−20 ± 4.0
20	37 ± 7.2	−19 ± 3.0
24	−12 ± 6.0	−11 ± 4.4
BM 17.0249	−84 ± 1.5	−50 ± 2.3

[a] ^{14}C-acetate incorporation into triglycerides and cholesterol in primary rat hepatocyte cultures; change in % of solvent-treated controls; DMSO: 0.1% final concentration, drug concentration: 30 μM; $\bar{x}$ ± SEM, n = 6 culture dishes from 3 preparations.

20.0 mmol) and 100 mL tetrahydrofurane) was added to a solution of 1,8-dibromooctane (16.3 g, 60.0 mmol) in 20 mL THF. A Grignard solution of phenylmagnesiumbromide prepared from magnesium (2.10 g), bromobenzene (11.31 g, 72.00 mmol) and 160 mL THF, 2 h reflux, was added at 0 °C from a dropping funnel within 1 h. The reaction mixture was stirred for 20 h at room temperature (r.t.) (dark colouring) and hydrolysed with 50 mL ammonium chloride solution. The mixture was extracted with 100 mL ethyl acetate and the organic phase washed twice with saturated sodium chloride and dried (Na_2SO_4). After removal of the solvent at reduced pressure vacuum distillation of the residue gave 12.2 g (61%) **2a** as a colourless oil, b.p. 110–120 °C/0.7 mbar. Under a nitrogen atmosphere butyllithium (29.0 mL, 72.0 mmol; 2.5 M in hexane) was added at −78 °C to a solution of diisopropylamine (7.27 g, 72.0 mmol) in 100 mL THF followed by dichloroacetic acid (4.64 g, 30.0 mmol) in 20 mL THF. The temperature of the resulting clear yellow enolate solution was maintained at −78 °C for 30 min and a solution of **2a** (9.94 g, 30.0 mmol) in 30 mL THF was added. The temperature was allowed to reach −30 °C slowly (an earlier formed precipitate disappeared) and then lowered to −50 °C again. When the mixture reached −30 °C it was quenched by the addition of 50 mL 3 N HCl and 200 mL ethyl acetate. The organic layer was washed twice with saturated sodium chloride, dried (Na_2SO_4) and the solvent was then evaporated. After purification by flash chromatography (eluent: petroleum ether/ethyl acetate 1:3, 1% acetic acid) acid **3a** was dissolved in ethyl acetate and the sodium salt precipitated by the addition of saturated sodium bicarbonate solution. The precipitate was collected, washed with petroleum ether and recrystallized twice from ethyl acetate. 3.50 g (35%) sodium salt of **3a**, m.p. 154–156 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.26–1.51 (m, 12H, CH_2), 2.25 (t, 2H, CH_2CCl_2), 2.58 (t, 2H, CH_2Ar, J = 7.7 Hz), 7.14–7.23 (m, 3H, o-, p-Ar–H), 7.25–7.28 (m, 2H, m-Ar–H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 25.8, 28.9, 29.1, 29.3, 31.4, 35.5, 40.8 (CH_2), 46.8 (CH_2CCl_2), 94.1 (CCl_2), 125.9, 128.5, 128.6 (Ar–CH), 142.7 (Ar–*C*–CH_2), 165.9 (C=O).

6.1.2. 2,2-Dichloro-14-phenyltetradecanoic acid 3c

As described for **2a, 2c** was obtained from 1,12-dibromododecane (19.7 g, 60.0 mmol), bromobenzene (11.31 g, 72.00 mmol), magnesium (2.10 g) and Li_2CuCl_4 (1.0 mmol; 0.1 M in THF). 12.2 g (61%) **2c**, as a colourless liquid, b.p. 130–140 °C/0.7 mbar. Diisopropylamine (7.27 g, 72.0 mmol), butyllithium (29.0 mL, 72.0 mmol; 2.5 M in hexane) and dichloroacetic acid (4.64 g, 30.0 mmol in THF) were added to a solution of **2c** (9.94 g, 30.0 mmol) at −78 °C. The temperature was allowed to reach −30 °C and then lowered again to −50 °C. On reaching 20 °C 50 mL 3 N HCl and 200 mL ethyl acetate were added and the mixture was washed twice with 150 mL 3 N HCl and saturated sodium chloride solution. The solution was then dried (Na_2SO_4) and the solvent evaporated. Purification was carried out by flash chromatography (eluent: petroleum ether/ethyl acetate 7:1, 1% acetic acid).

By addition of saturated $NaHCO_3$ to a solution of **3c** the sodium salt was precipitated, separated by filtration, washed twice with petroleum ether and recrystallized from ethyl acetate; 6.72 g (56%) of **3c**, colourless sodium salt, m.p. 171 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.09–1.34 (m, 16H, CH_2), 1.50–1.75 (m, 4H, CH_2), 2.08 (t, 2H, CH_2CCl_2), 2.41 (t, 2H, CH_2Ar, J = 7.8 Hz), 6.99–7.03 (m, 3H, o-, p-Ar–H), 7.06–7.10 (m, 2H, m-Ar–H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 21.2, 30.4, 30.6, 30.7, 30.8, 32.8, 36.9, 40.9, 41.2, 41.9, 42.2 (CH_2), 48.3 (CH_2CCl_2), 95.6 (CCl_2), 127.3, 129.9, 130.0 (Ar–CH), 144.0 (Ar–*C*–CH_2), 167.0 (C=O).

6.1.3. 2,2-Dichloro-7-(4-chlorophenyl)heptanoic acid 3d

As described for **2a, 2d** was obtained from 1,5-dibromopentane (13.8 g, 60.0 mmol), 4-bromo-1-chlorobenzene (13.8 g, 72.0 mmol), magnesium (1.95 g, 80.0 mmol), and Li_2CuCl_4 (10 mL, 1.0 mmol; 0.1 M in THF). 15.7 g (53%) **2d**, as a colourless liquid, b.p. 115–117 °C/0.05 mbar. Reaction of **2d** (5.00 g, 19.1 mmol) with dichloroacetic acid (9.81 g, 76.4 mmol) gave 4.7 g (79%) **3d** as a colourless oil after purification by flash chromatography (eluent: petroleum ether/ethyl acetate 10:1). The sodium salt was obtained by treatment with saturated $NaHCO_3$ solution. 4.7 g (74%), m.p. 158–162 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.30–1.54 (m, 6H, CH_2), 2.23 (t, 2H, CH_2CCl_2, J = 4.0 Hz), 2.58 (t, 2H, CH_2Ar, J = 7.5 Hz), 7.20, 7.31 (2d, 4H, Ar–H, J = 8.2 Hz).

^{13}C-NMR (DMSO-d_6): δ (ppm) 25.6, 28.5, 31.1, 34.6 (CH_2), 46.7 (CH_2CCl_2), 93.7 (CCl_2), 128.5, 130.5 (Ar–CH), 130.5 (Ar–*C*–CH_2), 141.5 (Ar–*C*–Cl), 166.3 (C=O).

Table III. Effects of ω-substituted alkyl carboxylic acids in diabetic ob/ob mice. [a]

Compound	Blood glucose % change (mg/100 mL)	Serum insulin % change (μU/mL)	Triglycerides % change (mg/100 mL)	NEFA % change (ME/L)
3a	–91	–44	–41	–28
	(136 ± 4)	(140 ± 19)	(76 ± 2)	(0.932 ± 0.06)
3b	–56	–22	–32	–25
	(185 ± 23)	(223 ± 36)	(84 ± 5)	(0.900 ± 0.11)
3c	–99	–65	–59	–39
	(122 ± 3)	(86 ± 12)	(79 ± 3)	(0.782 ± 0.03)
3d	–109	–95	36	–21
	(113 ± 4)	(18 ± 2)	(154 ± 11)	(1.144 ± 0.10)
3e	–106	–96	–52	–37
	(115 ± 4)	(17 ± 1)	(54 ± 3)	(0.907 ± 0.06)
3f	–76	–79	–66	–61
	(163 ± 16)	(35 ± 9)	(60 ± 4)	(0.631 ± 0.03)
3g	–42	–93	–42	–9
	(169 ± 16)	(27 ± 2)	(66 ± 4)	(1.323 ± 0.07)
4	–55	–21	–15	–18
	(140 ± 11)	(305 ± 60)	(122 ± 7)	(1.192 ± 0.10)
5	–53	–51	–63	–44
	(200 ± 26)	(155 ± 32)	(73 ± 3)	(0.755 ± 0.01)
6	–91	–47	–41	–31
	(135 ± 4)	(131 ± 15)	(76 ± 4)	(0.889 ± 0.04)
10a	–73	–35	–37	–32
	(159 ± 16)	(186 ± 27)	(78 ± 4)	(0.821 ± 0.04)
10b	–91	–31	–68	–48
	(133 ± 5)	(239 ± 39)	(68 ± 2)	(0.876 ± 0.05)
10c	–80	–85	–69	–55
	(148 ± 6)	(51 ± 10)	(67 ± 3)	(0.765 ± 0.05)
10d	–70	–91	–39	–21
	(145 ± 4)	(41 ± 7)	(70 ± 5)	(1.150 ± 0.07)
10e	–75	–77	–33	–15
	(141 ± 6)	(86 ± 10)	(76 ± 3)	(1.230 ± 0.08)
13	–90	–52	–45	–29
	(136 ± 9)	(119 ± 13)	(72 ± 3)	(0.914 ± 0.05)
16	–46	–88	–14	–1
	(165 ± 27)	(44 ± 8)	(97 ± 15)	(1.413 ± 0.24)
18	–98	–72	–72	–5
	(124 ± 4)	(107 ± 6)	(74 ± 4)	(1.104 ± 0.03)
20	–89	–81	–72	–8
	(138 ± 6)	(76 ± 9)	(74 ± 4)	(1.107 ± 0.07)
24	–80	–27	–40	43
	(149 ± 12)	(210 ± 40)	(74 ± 5)	(1.716 ± 0.09)

[a] Blood glucose, insulin, triglycerides and non-esterified fatty acids (NEFA) in the serum of male ob/ob mice after oral administration for 5 days; % change to vehicle-treated controls except glucose: lowering to normoglycaemia (120 mg/100 mL) is rated as 100%; absolute values in brackets; $\bar{x}$ ± SEM, n = 9–10.

6.1.4. 2,2-Dichloro-12-(4-chlorophenyl)dodecanoic acid ***3e***

20 mL of Li_2CuCl_4 (20 mL, 2.0 mmol; 0.1 M in THF) were added to a solution of 1,10-dibromodecane (40.0 g, 130 mmol in 110 mL THF). 100 mL 1 M 4-Chlorophenylmagnesium bromide solution (Aldrich) was then added in small portions over a period of 4 h at r.t. The mixture was stirred four 18 h, hydrolysed with 100 mL 3 N HCl, dissolved in 300 mL ethyl acetate and washed with 300 mL 3 N HCl, saturated NH_4Cl and NaCl. The organic

phase was dried (Na_2SO_4) and the solvent evaporated. The colourless product **2e** was fractionated in a vacuum, 8.0 g (24%) **2e**, b.p. 170–175 °C/0.8 mbar.

The colourless product **3e** was obtained by treatment of **2e** (8.00 g, 24.0 mmol) with dichloroacetic acid (6.45 g, 50.0 mmol) and recrystallization from petroleum ether at –30 °C. The sodium salt was prepared by dissolving the acid **3e** in 100 mL ethyl acetate. Saturated $NaHCO_3$ was added and the organic phase washed twice with NaCl and then dried (Na_2SO_4). After addition of petroleum ether the sodium salt precipitated overnight at r.t., m.p. > 250 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.28–1.51 (m, 16H, CH_2), 2.27 (t, 2H, CH_2CCl_2, J = 4.1 Hz), 2.54 (t, 2H, CH_2Ar, J = 7.5 Hz), 7.18, 7.28 (2d, 4H, Ar–H, J = 8.2 Hz).

^{13}C-NMR (DMSO-d_6): δ (ppm) 25.8, 28.9, 29.0, 29.3, 31.2, 34.8, 38.8, 39.2, 40.2 (CH_2), 46.8 (CH_2CCl_2), 93.8 (CCl_2), 128.4, 130.4 (Ar–CH), 130.5 (Ar–*C*–CH_2), 141.6 (Ar–*C*–Cl), 166.3 (C=O).

*6.1.5. 2,2-Dichloro-12-(4-methylthiophenyl)dodecanoic acid **3f***

In anology to **2a, 2f** was obtained from 1,10-dibromodecane (16.5 g, 55.0 mmol), 4-bromothioanisole (13.1 g, 64.2 mmol), magnesium (1.70 g, 70.0 mmol), Li_2CuCl_4 (10 mL, 1.0 mmol, 0.1 M in THF). 11.2 g (59%) **2f**. Reaction of **2f** (6.90 g, 20.0 mmol) with dichloroacetic acid (10.32 g, 80.00 mmol) gave 2.1 g (14%) **3f** after flash chromatography with gradient elution (eluent: heptane and than heptane/ethyl acetate 10:1). The sodium salt was prepared by treatment with NaOH and ether, m.p. 143 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.27–1.51 (m, 16H, CH_2), 2.27 (t, 2H CH_2CCl_2), 2.46 (s, 3H, SCH_3), 2.50 (t, 2H, CH_2Ar, J = 7.3 Hz), 7.12–7.19 (2d, 4H, Ar–H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 15.4 (SCH_3), 25.8, 28.9, 29.0, 29.2, 29.3, 29.4, 31.3, 34.9, 38.8 (CH_2), 46.9 (CH_2CCl_2), 94.1 (CCl_2), 126.6, 129.2 (Ar–CH), 135.0 (Ar–*C*–CH_2), 139.5 (Ar–*C*–S), 165.9 (C=O).

*6.1.6. 2,2-Dichloro-12-(4-tert-butylphenyl)dodecanoic acid **3g***

In analogy to **2a, 2g** was obtained from 1,10-dibromodecane (16.5 g, 55.0 mmol), 4-*tert*-butylbromobenzene (13.7 g, 64.2 mmol), magnesium (1.7 g, 70 mmol), Li_2CuCl_4 (10 mL, 1.0 mmol; 0.1 M in THF) after flash chromatography (eluent: ethyl acetate/heptane 1:10). 4.6 g (24%) as a light yellow oil, b.p. 134 °C/0.2 mbar. Reaction of **2g** (4.60 g, 13.0 mmol) with dichloroacetic acid (6.70 g, 52.0 mmol) gave 1.1 g (22%) **3g**, m.p. 46–48 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 0.90–1.52 (m, 16H, CH_2), 1.39 (s, 9H, $(CH_3)_3C$), 2.47 (t, 2H, CH_2CCl_2), 2.59 (t, 2H, CH_2Ar), 7.12, 7.34 (2d, 4H, Ar–H), 8.97 (s, 1H, COOH).

*6.1.7. 2,2-Dichloro-12-(2-naphthyl)dodecanoic acid **5***

As described for **2a**, 3.7 g (20%) of 1-bromo-10-(2-naphthyl)decane (**25**) were obtained as light yellow oil from 1,10-dibromodecane (16.5 g, 55.0 mmol), 2-bromonaphthalene (13.3 g, 64.2 mmol), magnesium (1.7 g, 70 mmol) and Li_2CuCl_4 (10 mL, 1 mmol, 0.1 M in THF). 3.5 g (10.0 mmol) of **25** were reacted with dichloroacetic acid (5.16 g, 40.0 mmol) to give 3.1 g (79%) **5**, m.p. 66–67 °C after purification by flash chromatography (eluent: ethyl acetate/heptane, 1:10).

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.30–1.72 (m, 16H, CH_2), 2.44 (t, 2H, CH_2CCl_2), 2.77 (t, 2H, CH_2Ar), 7.26–7.80 (m, 7H, naphthyl).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.1, 26.0, 28.9, 29.3, 29.4, 29.5, 29.6, 31.4, 36.2 (CH_2), 45.0 (CH_2CCl_2), 84.3 (CCl_2), 125.0, 125.9, 126.3, 127.4, 127.5,127.7, 127.8, 132.0, 133.7 (naphthyl), 170.4 (C=O).

*6.1.8. 2,2-Dichloro-12-cyclohexyldodecanoic acid **6***

In analogy to example **3a** compound **6** was prepared from Li_2CuCl_4 (10 mL, 1.0 mmol), 1,10-dibromodecane (18.0 mg, 60.0 mmol) in 20 mL THF, magnesium (2.10 g) and cyclohexylbromide (11.7 g, 72.0 mmol). After 20 h 50 mL saturated ammonium chloride solution and 100 mL ethyl acetate were added and the phases separated. The organic phase was washed with saturated sodium chloride solution and dried (Na_2SO_4). The solvent was evaporated and the residue fractionated by vacuum distillation. 9.62 g (53%) of 1-bromo-10-cyclohexyldecane (**26**), b.p. 103–105 °C/0.7 mbar were obtained as a colourless liquid. Reaction of **26** (9.10 g, 30.0 mmol) with dichloroacetic acid (4.64 g, 36.0 mmol) gave 4.88 g (46%) of **6**, m.p. 67–68 °C as a colourless oil after flash chromatography (eluent: petroleum ether/ethyl acetate, 1:3; 1% acetic acid) and recrystallization at low temperatures from toluene.

^{1}H-NMR ($CDCl_3$): δ (ppm) 0.75–0.95 (m, 2H), 1.00–1.45 (m, 20H), 1.50–1.80 (m, 7H), 2.44 (m, 2H, CH_2CCl_2), 10.87 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.1, 26.5, 26.8, 29.9, 28.9, 29.3, 29.5, 29.6, 29.7, 30.0, 33.5, 37.6, 45.0 (CH_2), 37.7 (CH), 84.2 (CCl_2), 171.6 (C=O).

*6.1.9. 2,2-Dichloro-12-phenoxydodecanoic acid **10a***

Phenol (2.90 g, 30.8 mmol) and 1,10-dibromodecane (9.00 g, 30.0 mmol) were added to a solution of sodium ethanolate prepared from sodium hydride (1.20 g, 30.0 mmol) and 30 mL ethanol. The light yellow solution was heated under reflux. After 30 min a precipitate became visible. After 6 h the mixture was cooled, 300 mL ethyl acetate were added and the organic layer was washed three times with 200 mL saturated NaCl. After drying (Na_2SO_4) and evaporation the residue was dissolved in ethanol and cooled to 4 °C for 24 h. The precipitated product **9a** was filtered off and washed with cold ethanol; 6.00 g (63%), m.p. 62–64 °C were obtained.

A solution of **9a** (5.84 g, 18.6 mmol) in 20 mL THF was added at –78 °C to an enolate solution prepared from diisopropylamine (7.60 g, 75.0 mmol), butyllithium (46 mL, 74 mmol; 1.6 M in hexane) and dichloroacetic acid (4.81 g, 37.2 mmol) in 80 mL THF. The temperature was allowed to reach –30 °C and then lowered again to –50 °C. After reaching –20 °C, 50 mL 3N HCl and 200 mL ethyl acetate were added and the mixture was washed twice with 150 mL 3N HCl and twice with saturated NaCl. The mixture was dried (Na_2SO_4) and the solvent evaporated. Flash chomatography (eluent: petroleum ether/isopropanol 96:4; 0.5% acetic acid) gave 4.25 g (63%) **10a**, m.p. 58–60 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.31–1.78 (m, 16H, CH_2), 2.43 (t, 2H, CH_2CCl_2), 3.96 (t, 2H, OCH_2), 6.88–7.23 (m, 5H, Ar–H).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.0, 26.0, 28.8, 29.1, 29.2, 29.3, 29.4, 45.0 (CH_2), 68.0 (OCH_2), 84.3 (CCl_2), 114.6, 120.6, 129.4 (Ar–CH), 159.0 (Ar–*C*–O), 170.9 (C=O).

*6.1.10. 2,2-Dichloro-12-(4-methylphenoxy)dodecanoic acid **10b***

4-Methylphenol (6.5 g, 60 mmol) and 1,10-dibromodecane (18.0 g, 60.0 mmol) were added to a solution of sodium ethanolate,

prepared from sodium hydride (6.5 g, 60 mmol) in 60 mL ethanol. The mixture was heated for 6 h under reflux and a colourless precipitate was formed. 200 mL 3 N HCl and 200 mL ethyl acetate were added, the mixture washed twice with NaCl, then dried (Na_2SO_4) and the solvent evaporated. The diphenyl ether precipitated after addition of toluene. The filtrate was distilled and the fraction at 150–160 °C/1.3 mbar was collected. Recrystallization from ethyl acetate gave 9.75 g **9b**. The product **10b** resulted in the same manner as **10a** from dichloroacetic acid (5.15 g, 40.0 mmol) and **9b** (9.5 g, 29 mmol) and was purified by flash chromatography (eluent: petroleum ether/isopropanol 9:1, 1% acetic acid). Petroleum ether was added to the oil obtained and the sodium salt precipitated with saturated $NaHCO_3$. After recrystallization from ethyl acetate and addition of 3 N HCl the free acid was extracted with ethyl acetate, dried (Na_2SO_4) and the solvent evaporated. Recrystallization from petroleum ether gave 2.4 g (22%) of **10b**, m.p. 67–68 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.20–1.87 (m, 16H, CH_2), 2.45 (m, 2H, CH_2CCl_2), 3.94 (t, 2H, OCH_2), 6.81, 7.08 (2m, 4H, Ar–H), 9.0 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 20.4 (CH_3Ar), 25.0, 26.0, 28.8, 29.2, 29.3, 29.4 (CH_2), 44.9 (CH_2CCl_2), 68.2 (CH_2O), 84.3 (CCl_2), 114.4, 129.8 (Ar–*C*–H), 129.8 (Ar–*C*–CH_3), 156.8 (Ar–*C*–O), 170.59 (C=O).

6.1.11. 2,2-Dichloro-12-(4-chlorophenoxy)dodecanoic acid ***10c***

The compound was synthesized in the same way as **10b**. 13.6 g (65%) **9c** were obtained from 4-chlorophenol (7.7 g, 60 mmol) and 1,10-dibromodecane (18.0 g, 60.0 mmol). **9c** (13.3 g, 38.0 mmol) and dichloroacetic acid (13.3 g, 38.0 mmol) were reacted to give 5.9 g (50%) of **10c**, m.p. 63–64 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.10–1.50 (m, 12H, CH_2), 1.50–1.75 (m, 2H, CH_2), 1.77 (t, 2H, CH_2), 2.44 (m, 2H, CH_2CCl_2), 3.93 (t, 2H, CH_2O), 6.82, 7.22 (2m, 4H, Ar–H), 8.00 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.0, 26.0, 28.8, 29.2, 29.3, 29.4 (CH_2), 45.0 (CH_2CCl_2), 68.4 (CH_2O), 84.2 (CCl_2), 115.8, 129.26 (Ar–*C*–H), 125.4 (Ar–*C*–Cl), 157.7 (Ar–*C*–O), 170.3 (C=O).

6.1.12. 2,2-Dichloro-12-(4-tert-butylphenoxy)dodecanoic acid ***10d***

As described for compound **9b**, **9d** was obtained from 4-*tert*-butylphenol (9.75 g, 65.0 mmol), sodium hydride (1.60 g, 65.0 mmol), 1,10-dibromodecane (21.0 g, 70.0 mmol) after distillation at 170–175 °C/0.06 mbar; 16.1 g (67%) as a yellow oil. Reaction of **9d** (6.8 g, 20 mmol) with dichloroacetic acid (10.3 g, 80.0 mmol) gave 2.8 g (35%) **10d**. The sodium salt, m.p. 178 °C, was prepared by treatment of **10d** with powdered NaOH in ethanol.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.03–1.40 (m, 16H, CH_2), 2.09 (s, 9H, $(CH_3)_3C$), 2.30 (t, 2H, CH_2CCl_2), 3.49 (t, 2H, OCH_2), 6.89–7.08 (2d, 4H, Ar–H).

6.1.13. 2,2-Dichloro-12-(4-methoxyphenoxy)dodecanoic acid ***10e***

In analogy to compound **9b**, **9e** was obtained from 4-methoxyphenol (7.5 g, 60 mmol) and 1,10-dibromodecane (18 g, 60 mmol); 8.8 g (43%), m.p. 64–66 °C. An enolate solution prepared from lithium diisopropylamide (80.0 mmol) and dichloroacetic acid (5.15 g, 40.0 mmol) in 50 mL THF was added to **9e** (7.0 g, 20 mmol; in 20 mL THF) in 1 h at –78 °C. After stirring for 1 h it was hydrolysed with 3 N HCl, 200 mL ethyl acetate were added and the mixture was washed twice with 3 N HCl and saturated NaCl solution. The organic phase was evaporated under vacuum and the remaining oil dissolved in petroleum ether. A saturated $NaHCO_3$ solution was added until no more carbon dioxide was formed. After 30 min the precipitate obtained was filtered off and recrystallized from ethyl acetate. The colourless salt was dissolved in ethyl acetate, acidified with 3N HCl and the organic phase washed with saturated NaCl. The product **10e**, 1.6 g (20%), m.p. 68–69 °C, resulted after drying (Na_2SO_4), evaporation and recrystallization from petroleum ether.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.15–1.55 (m, 12H, CH_2), 1.62 (m, 2H, CH_2), 1.76 (q, 2H, CH_2, J = 7.3 Hz), 2.44 (m, 2H, CH_2CCl2), 3.78 (s, 3H, OCH_3), 3.92 (t, 2H, OCH_2, J = 6.6 Hz), 6.85 (s, 4H, Ar–H), 10.3 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.1, 26.0, 28.8, 29.2, 29.3, 29.4 (CH_2), 45.0 (CH_2CCl_2), 55.9 (CH_3O), 69.0 (OCH_2), 84.4 (CCl_2), 114.8, 115.7 (Ar–CH), 153.3, 153.7 (Ar–*C*–O), 170.3 (C=O).

6.1.14. 2,2-Dichloro-7-(5-phenylpentoxy)heptanoic acid ***13***

5-Phenyl-1-pentanol (2.40 g, 14.6 mmol) was added dropwise to a suspension of NaH (610 mg, 15.0 mmol; 60% in white oil) in 5 mL THF. After the development of H_2 finished 1,5-dibromopentane (9.6 mL, 33 mmol) was added and the mixture heated for 6 h at 80 °C. After flash filtration (eluent: petroleum ether) and flash chromatography (eluent: petroleum ether) 8.3 g of the colourless liquid **12** were obtained. **12** (3.03 g, 9.67 mmol) was reacted with dichloroacetic acid (1.93 g, 15.0 mmol). After flash chromatography (eluent: petroleum ether/ethyl acetate, 9:1; 1% acetic acid) and recrystallization from toluene, 1.6 g (43%) of **13**, m.p. 83–84 °C were obtained.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.25–1.50 (m, 4H, CH_2), 1.50–1.85 (m, 8H, CH_2), 2.35–2.58 (m, 2H, CH_2CCl_2), 2.61 (t, 2H, CH_2Ar, J = 7.6 Hz), 3.44 (t, 4H, CH_2O–CH_2, J = 6.6 Hz), 7.15–7.19 (m, 3H, o-, p-Ar–H), 7.24–7.29 (m, 2H, m-Ar–H), 7.67 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.1, 25.4, 25.7, 29.1, 29.1, 31.3, 35.9, 45.1 (CH_2), 70.7, 71.1 (CH_2O–CH_2), 84.7 (CCl_2), 125.7, 128.3, 28.4 (Ar–CH), 142.6 (Ar–*C*–CH_2), 168.3 (C=O).

6.1.15. 2,2-Dichloro-14-phenylthiotetradecanoic acid ***16***

K_2CO_3 (3.46 g, 25.0 mmol) and thiophenol (2.75 g, 25.0 mmol) were added to a solution of 14-bromo-2,2-dichlorotetradecanoic acid ethyl ester **14** (10.1 g, 25.0 mmol) in 200 mL DMF. The mixture was stirred for 12 h at r.t., 300 mL H_2O were added and the mixture was extracted with ether. After washing with H_2O, drying (Na_2SO_4), solvent evaporation in vacuo and flash chromatography (eluent: heptane/toluene 5:1) 6.62 g (61%) of compound **15** resulted as a colourless oil. **15** (1.5 g, 3.5 mmol) was dissolved in 3.8 mL ethanol and extracted with 3.8 mL 1 N KOH. The precipitate **16** was dissolved in 20 mL of a solution of ethanol/H_2O 1:1. After stirring for 5 h 1 mL 1 N KOH was added and stirring continued for 6 h. After acidification with 2 N HCl the mixture was extracted with ether, dried ($MgSO_4$) and the solvent evaporated, 1.18 g (92%) **16**, m.p. 74 °C were obtained.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.29–1.52 (m, 20H, CH_2), 2.45 (t, 2H, CH_2CCl_2), 2.91 (t, 2H, SCH_2), 7.13–7.36 (m, 5H, Ar–H).

6.1.16. 2,2-Dichloro-14-phenylsulphinyltetradecanoic acid ***18***

m-Chloroperbenzoic acid (0.72 g, 4.15 mmol) dissolved in 15 mL dichloromethane was added at –5 °C to a solution of

2,2-dichloro-14-phenylthiotetradecanoic acid ethyl ester **15** (1.80 g, 4.15 mmol) in 30 mL dichloromethane. Within 2 h, r.t. was reached and the organic phase was washed with $NaHCO_3$ and H_2O. After drying ($MgSO_4$), evaporation of the solvent and purification by flash chromatography (eluent: heptane/ethyl acetate 2:1) 1.24 g (66%) of sulphinylester **17** resulted as a colourless oil. Compound **17** (0.46 g, 1.02 mmol) was stirred with 2.0 mL ethanol and 2.0 mL 1 N KOH for 2 h at r.t. The mixture was acidified with 2 N HCl, extracted with ether, dried (Na_2SO_4) and the solvent evaporated. The residue was kept at 8 °C for 12 h. 0.41 g (95%), m.p. 68 °C, of the crystalline compound **18** resulted.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.29–1.80 (m, 20H, CH_2), 2.47 (t, 2H, CH_2CCl_2), 2.92 (m, 2H, $SOCH_2$), 7.51–7.68 (m, 5H, Ar–H).

*6.1.17. 2,2-Dichloro-14-phenylsulphonyltetradecanoic acid **20***

4.5 mL 30% Hydrogenic peroxide were added to a solution of 2,2-dichloro-14-phenylthiotetradecanoic acid ethyl ester **15** (1.50 g, 3.46 mmol) in 15 mL acetic acid. After stirring for 48 h the mixture was poured into ice water. After extraction with ether, drying (Na_2SO_4) and evaporation of the solvent 1.23 g (77%) of oil **19** were obtained. **19** (1.22 g, 2.62 mmol) was added to 5.2 mL ethanol and 5.2 mL 1 N KOH and stirred for 3 h. The mixture was cooled to 0 °C and acidified with 2 N HCl. The precipitated product **20** was filtered off, washed with water and isohexane and dried in vacuo. 1.12 g (97%) of **20**, m.p. 69–71 °C were obtained.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.26–1.77 (m, 20H, CH_2), 2.36 (m, 2H, CH_2CCl_2), 3.09 (t, 2H, SO_2CH_2), 7.52–7.68 (m, 3H, o-, p-Ar–H), 7.88 (t, 2H, m-Ar–H).

*6.1.18. 2,2-Dichloro-12-phenyl-11-dodecenoic acid **24***

1,9-Dibromononane (103.0 g, 0.360 mmol) (**21**) was stirred at 120 °C. Within 8 h a solution of triphenylphosphine (11.8 g, 0.045 mol) in 120 mL toluene was added. After 10 h the solution was cooled, the supernatant decanted, stirred with isohexane at 60 °C and evaporated under nitrogen. 22.4 g (91%) of **22** were obtained. 200 mL THF were added to **22** (2.13 g, 3.80 mmol) and cooled to –78 °C under nitrogen. Butyllithium (1.53 mL, 3.60 mmol; 2.45 N in hexane) was added and the mixture was then stirred again for 30 min at –78 °C. After addition of freshly distilled benzaldehyde (0.40 mL, 4.00 mmol) the temperature was allowed to rise to 0 °C and 5 mL saturated ammonium chloride solution were added. After dropwise addition of 2 N HCl the organic phase was separated and the aqueous phase extracted with ether. The ether phase was washed with water, dried ($MgSO_4$) and purified by flash chromatography (eluent: heptane), 0.86 g (73%) **23**. Compound **23** (4.52 g, 15.3 mmol) was reacted with dichloroacetic acid (4.34 g, 33.7 mmol) and hydrolysed at –40 °C with 6 N HCl. A precipitate was dissolved by addition of a few mL of water. Then the organic phase was separated, washed with water, dried ($MgSO_4$) and the solvent evaporated. After purification by flash chromatography (eluent: heptane/ethyl acetate 10:1) 2.32 g (45%) **24**, m.p. 50–52 °C were obtained.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.32–1.61 (m, 14H, CH_2), 2.88 (dq, 2H, CH=CH–CH_2) 2.39 (m, 2H, CH_2CCl_2), 5.65 (dt, Ar–CH=C*H*–CH_2, J = 7.25 Hz; J = 11.7 Hz), 6.38 (td, Ar–C*H*=CH, J = 11.67 Hz; J = 1.68 Hz), 7.28 (m, 5H, Ar–H).

*6.1.19. 2,2-Dichloro-12-phenyldodecanoic acid **3b***

2,2-Dichloro-12-phenyl-11-dodecenoic acid (1.09 g, 3.18 mmol) **24** was dissolved in 300 mL THF. After addition of 200 mg 10%/Pd/$BaSO_4$ the mixture was hydrogenated at –40 °C for 40 min. The catalyst was separated and the remaining solution evaporated. The oil obtained (100 mg, 0.29 mmol) was dissolved in 1 mL ethanol, cooled in an ice bath and a solution of NaOH (12.0 mg, 0.29 mmol) in 1 mL ethanol was added. The sodium salt was precipitated by addition of ether and was cooled for 12 h at 4 °C. The precipitate was filtered off, washed with cold ether and dried in vacuum, m.p. 157–159 °C.

^{1}H-NMR (DMSO-d_6): δ (ppm) 1.29–1.51 (m, 16H, CH_2), 2.28 (t, 2H, CH_2CCl_2), 2.60 (t, 2H, CH_2Ar, J = 7.7 Hz), 7.16–7.18 (m, 3H, o-, p-Ar–H), 7.27–7.30 (m, 2H, m-Ar–H).

^{13}C-NMR (DMSO-d_6): δ (ppm) 25.8, 28.9, 29.0, 29.2, 29.3, 31.4, 35.5, 38.8, 40.5, 46.9 (CH_2), 94.5 (CCl_2), 125.9, 128.5, 128.6 (Ar–CH), 142.7 (Ar–*C*–CH_2), 165.2 (C=O).

*6.1.20. 2,2-Dichloro-12-(4-carboxyphenyl)dodecanoic acid **4***

*6.1.20.1. 1-Bromo-10-(4-carboxyphenyl)decane **27***: Within 1 h a solution of 4-methylbenzoic acid (20.1 g, 148 mmol) in 150 mL THF was added dropwise to a solution of 300 mmol LDA in 300 mL THF at –70 °C. Stirring was continued for 1 h at the same temperature and followed by the addition of 1,9-dibromononane (42.4 g, 148 mmol). The mixture was allowed to warm to r.t. overnight, acidified with 3 N HCl and then extracted with 500 mL ethyl acetate. The organic layer was washed with 3 N HCl and saturated NaCl. The combined aqueous phase was reextracted with 300 mL ethyl acetate and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residue was treated with ethyl acetate, filtered to remove precipitate and the filtrate purified by flash chromatography. After elution of dibromononane (14.2 g) with petroleum ether **27** was eluted with petroleum ether/ethyl acetate (8:2), 1% acetic acid. Recrystallization from petroleum ether yielded 13.6 g (27%) **27**, m.p. 88–92 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.15–1.52 (m, 14H, CH_2), 1.64 (m, 2H), 1.85 (t, 2H, J = 7.0 Hz), 2.68 (t, 2H, CH_2Ar, J = 7.7 Hz), 3.41 (t, 2H, CH_2Br, J = 6.8 Hz), 7.28, 8.03 (2d, 4H, Ar–H, J = 8.2 Hz).

*6.1.20.2. 1-Bromo-10-(4-tert-butyloxycarbonylphenyl)decane **28***: A mixture of **27** (13.6 g, 39.8 mmol) and 25 mL thionyl chloride was heated under reflux for 2 h until evolution of gas stopped. Excess thionyl chloride was distilled off and the residue heated to 100 °C at 10 mbar. The resulting acid chloride was dissolved in 50 mL THF, added dropwise at 0 °C to a suspension of NaH (1.6 g, 47 mmol; 60% in white oil) and *tert*-butyl alcohol (3.5 g, 47 mmol) in 200 mL THF. After stirring for 18 h, the mixture was hydrolysed with 10 mL water and 300 mL ethyl acetate. The organic phase was washed with saturated ammonium chloride solution and water, dried (Na_2SO_4) and the solvent removed in vacuo. Flash chromatography (petroleum ether) gave 12.3 g (78%) **28** as a yellow oil.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.20–1.50 (m, 14H, CH_2), 1.50–1.70 (m, 2H), 1.59 (s, 9H, $C(CH_3)_3$), 1.84 (t, 2H, J = 7.0 Hz), 2.64 (t, 2H, CH_2Ar, J = 7.7 Hz), 3.40 (t, 2H, CH_2Br, J = 6.8 Hz), 7.21, 7.90 (2d, 4H, Ar–H, J = 8.2 Hz).

*6.1.20.3. 2,2-Dichloro-12-(4-tert-butyloxycarbonylphenyl)dodecanoic acid **29***: **28** (12.2 g, 30.7 mmol) was added to an enolate solution prepared from LDA (120 mmol) und dichloroacetic acid (7.73 g, 60.0 mmol) in 150 mL THF at –70 °C. The mixture was allowed to reach r.t. overnight, then hydrolysed with 3 N HCl and 300 mL ethyl acetate. The organic layer was washed with 3 N HCl

and saturated sodium chloride solution. The organic phase was dried (Na_2SO_4), concentrated, dissolved in petroleum ether and shaken with saturated sodium bicarbonate solution. The clear petroleum ether layer was discarded and the heterogenous aqeous phase was extracted with 3 × 400 mL ethyl acetate. The combined ethyl acetate solution was dried and evaporated and the residue was recrystallized from ethyl acetate. The resulting sodium salt was dissolved in ethyl acetate and 3 N HCl was added. The organic phase was washed with saturated sodium chloride solution, dried (Na_2SO_4) and the solvent removed. Flash chromatography (petroleum ether/ethyl acetate 9:1; 1% acetic acid) and recrystallization from petroleum ether gave 4.5 g (33%) **29**, m.p. 93–94 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 1.15–1.45 (m, 14H), 1.45–1.70 (m, 11H, one s, 9H, $C(CH_3)_3$ at 1.59), 2.41.2.46 (m, 2H, CH_2CCl_2), 2.64 (t, 2H, CH_2Ar, J = 7.6 Hz), 7.21, 7.90 (2d, 4H, Ar–H, J = 8.2 Hz), 10.03 (s, 1H, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 25.1, 28.9, 29.0, 29.2, 29.2, 29.3, 29.4, 31.1, 35.9, 45,1 (CH_2), 28.2 ($C(CH_3)_3$), 81.3 ($OC(CH_3)_3$), 84.5 (CCl_2), 128.4, 129.6 (Ar–CH), 129.3, 148.1 (Ar–CC), 166.7, 169.7 (C=O).

6.1.20.4. 2,2-Dichloro-12-(4-carboxyphenyl)dodecanoic acid ***4***: **29** (2.45 g, 5.54 mmol) was dissolved in 50 mL of a 4 N solution of HCl in dioxane and heated for 12 h at reflux. After removal of the solvent in a vacuum the residue was recrystallized twice from petroleum ether/ethyl acetate. 2.05 g (95%) **4** as colourless needles were obtained, m.p. 122–128 °C.

^{1}H-NMR ($CDCl_3$): δ (ppm) 0.95–1.35 (m, 12H, CH_2), 1.35–1.65 (m, 4H, CH_2), 2.20–2.40 (m, 2H, CH_2CCl_2), 2.56 (t, 2H, CH_2Ar, J = 7.6 Hz), 7.15, 7.81 (2d, 4H, Ar–H, J = 8.2 Hz), 9.5–10.8 (s, COOH).

^{13}C-NMR ($CDCl_3$): δ (ppm) 24.6, 28.3, 28.6, 28.6, 28.8, 28.8, 30.6, 35.3, 44.7 (CH_2), 85.6 (CCl_2), 127.9, 129.2 (Ar–CH), 128.0, 147.5 (Ar–CC), 166.9, 167.6 (C=O).

6.2. Pharmacological methods

6.2.1. Chemicals

2-^{14}C-acetate, sodium salt, was obtained from Amersham Buchler, Braunschweig, Germany; Aqualuma from Baker, Gross-Gerau, Germany. The chemicals and media required for cell culture were obtained from Boehringer Mannheim, unless otherwise stated. All other chemicals were obtained in the necessary degrees of purity from the usual chemical suppliers. The columns packed with large pore kieselgur were supplied by Merck, Darmstadt, Germany.

6.2.2. Cell cultures

Primary hepatocytes were obtained from male Sprague–Dawley rats using the collagenase recirculation technique modified by Berry and Friend [32] and cultivated as a monolayer in Dulbecco's modified Eagle's medium [33] with the following additives: 16.5% fetal calf serum, L-glutamine (4 mmol), ornithine (0.4 mmol), insulin CS (0.25 IU/mL, bovine insulin, Boehringer Mannheim), streptomycin (100 μg/mL) and penicillin (100 IU/mL). After 16 h, the medium was exchanged for a lipid-free medium with addition of 2-^{14}C-acetate (37 kBq/mL) and the test compound dissolved in DMSO (0.1% final concentration) and the culture was incubated for a further 48 h. The monolayer and medium were treated with ultrasound and proteins were denaturated with ethanol (96% + 0.5% acetic acid, 2:1, v/v). An aliquot (1 mL) was eluted with n-heptane, evaporated to dryness and the residue dissolved in ethanol/acetone (50 μL, 1:1, v/v). After saponification with ethanolic KOH (250 μL, 0.5 M) and neutralization with acetic acid in ethanol (250 μL, 0.5 M) cholesterol was precipitated with 500 μL digitonin (1% dissolved in ethanol 80%). The mixture was allowed to precipitate at 4 °C for 16 h and centrifuged (20 min, 5000 rpm). The radioactivity in the supernatant (1 mL) was measured with 4.5 mL Aqualuma in a fluid scintillation spectrometer (Packard Tricarb 460 C) [34]. The pellet was dissolved in 3 mL Aqualuma to measure the radioactivity.

6.2.3. Animals and treatment

Male ob/ob mice (C57 BL /6J) from Jackson Laboritries, Bar Harbor, ME, USA, and Sprague–Dawley rats from Charles River, Kisslegg, Germany, were used. The animals were kept at 23 ± 1 °C, with a 12 h light/dark cycle (light at 6 a.m. to 6 p.m.). They were allowed to adapt for 12 days after arrival, housed under controlled conditions with standard food and water ad libitum. The substances were suspended in an aqueous sodium carboxymethylcellulose (1%) and administered orally (100 mg/kg/day) for 5 days; the controls received the same amounts of vehicle (10 mL/kg).

6.2.4. Blood sampling

For glucose determinations blood samples were taken from the tail tip of mice on day 0 before the first administration and on day 5, 2 h after the last administration. For all other serum parameters blood was collected by opening the neck vessels at the end of the experiment.

6.2.5. Determination of blood and serum parameters

Blood glucose was measured using the hexokinase method without deproteinization [35]. Triglycerides in serum were determined enzymatically [36]. Non-esterified fatty acids were measured using acylCoA synthase and acylCoA oxydase with a palmitic acid standard. The resulting hydrogen peroxide of the reaction gives a red dye in the presence of peroxidase.

Serum insulin levels in mice were assayed with an ELISA insulin test kit. All enzymes and chemicals required were purchased from Boehringer Mannheim.

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