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Carboxylic acids and skeletal muscle chloride channel conductance: effects on the biological activity induced by the introduction of an aryloxyalkyl group α to the carboxylic function of 4-chloro-phenoxyacetic acid

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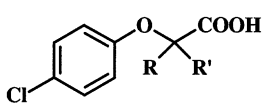
Abstract

2-(4-Chloro-phenoxy)propanoic and 2-(4-chloro-phenoxy)butanoic acids are compounds known to block chloride membrane conductance in rat striated muscle by interaction with a specific receptor. In the present study, a series of chiral analogues has been prepared and tested to evaluate the influence of a second aryloxy moiety introduced in the side-chain at a variable distance from the stereogenic centre. The results show that this chemical modification is detrimental for biological activity which, however, is increased by lengthening the alkyl chain up to three methylenic groups, then decreases to remain constant in the next analogues of the series. A possible explanation for this is proposed on the basis of steric effects and/or different approach of the molecules to the receptor.

Keywords: Aryloxyalkanoic acids; Chloride channel conductance; Rat skeletal muscle; Myotonic-inducing effects

1. Introduction

In skeletal muscle, 65–85% of the resting membrane conductance is due to chloride ions [1]. This large chloride conductance (gCl) stabilizes the resting membrane potential of mammalian muscle. In fact, muscles with abnormally low gCl can become hyperexcitable and produce trains of action potentials as observed in some forms of hereditary myotonia of goats [2] or humans and in myotonia produced by certain drugs [3–6]. In spite of the important role of resting gCl in mammalian muscle excitability, relatively few studies are available on the molecular mechanism underlying this function.



1. R = R' = CH_3
2. R = H; R' = CH_3
3. R = H; R' = C_2H_5

Fig. 1. Clofibric acid (**1**) and two of its analogues, 2-(4-chloro-phenoxy)propanoic acid (**2**) and 2-(4-chloro-phenoxy)butanoic acid (**3**).

In the past, clofibric acid [2-(4-chloro-phenoxy)-2-methyl-propanoic acid] (**1**) (Fig. 1), the active metabolite of the hypolipidemic drug clofibrate, has been shown to specifically decrease membrane gCl of rat skeletal muscle [7,8]. On the basis of these results, we introduced various chemical modifications in the molecular structure of clofibric acid and found out that, among the numerous derivatives prepared, only chiral 2-(4-chloro-phenoxy)propanoic acid (**2**) and 2-(4-chloro-phenoxy)butanoic acid (**3**) (Fig. 1) maintain a high activity in reducing gCl.

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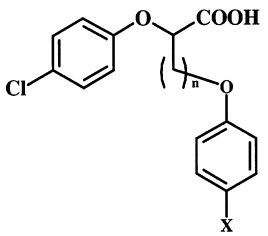


4a. X = Cl; n = 1 **4d. X = Cl; n = 4**
4b. X = Cl; n = 2 **4e. X = Cl; n = 5**
4c. X = Cl; n = 3 **4f. X = MeO; n = 3**

Fig. 2. Clofibric acid chiral analogues with an aryloxyalkyl group alpha to the carboxylic function.

In these compounds, also, the absolute configuration exerts a strong influence on the activity, with *S*-enantiomers being much more potent than *R*-enantiomers and clofibric acid itself [9]. On the contrary, *R*-enantiomers produce a biphasic effect on chloride channel conductance, increasing gCl at low concentrations and decreasing it at higher concentrations. These data allow the hypothesis of the existance of two opposing receptor populations controlling chloride ion flux: *S*-isomers would act as full agonists on an inhibitory site, whereas *R*-isomers as full agonists on both the inhibitory and excitatory sites [10,11].

In order to obtain more information on the structural requirements allowing α-aryloxyalkanoic acids to interact with these receptors, we focused on compounds **4a**–**f** (Fig. 2) in which the substituent on the stereogenic centre contains a second phenoxy group variably distanced from the stereogenic centre itself. We decided to test these compounds, recently claimed in a patent as hypolipidemic agents [12], to evaluate the possibility that these clofibrate-like drugs were able, in the same way, to interfere with gCl and, if so, to assess if a second aryloxy moiety could represent an additional interaction site with the receptor.

2. Chemistry

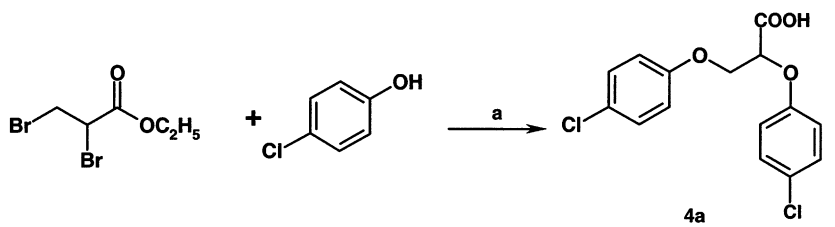
Compound **4a** [13] was prepared by simply refluxing a mixture of 4-chlorophenol and ethyl 2,3-dibromopropanoate in the presence of NaOH (Scheme 1).

A different synthetic pathway was followed for the preparation of acids **4b**–**f** [12]. As shown in Scheme 2, diethyl 2-(4-chloro-phenoxy)malonate (**5**) was reacted with the suitable aryloxyalkylbromides **6b**–**f** and the condensation products hydrolyzed and decarboxylated to give the desired compounds.

Starting materials **5** and **6b**–**f** were obtained as reported in Scheme 3, the former by reacting diethyl chloromalonate with sodium 4-chlorophenate in refluxing acetone, the latter by treating a mixture of phenol and alkyldibromide with a boiling NaOH solution, according to a procedure reported in literature for compound **6c** [14].

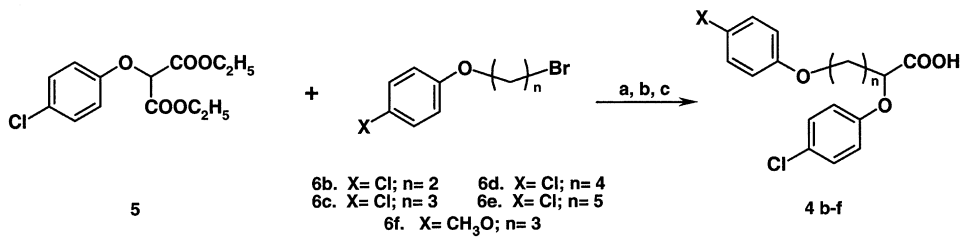
3. Results and discussion

The effects of in vitro application of these new synthesized clofibric acid derivatives on gCl of rat



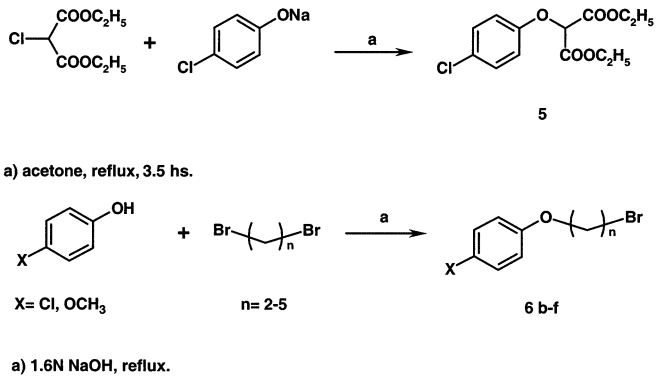
a) NaOH, reflux, 3 hs.

Scheme 1.



a) NaH 95%, dry DMF, 55°C, 20hs; b) NaOH, EtOH 95%, reflux, 4hs; c) 160°C, 2hs.

Scheme 2.



Scheme 3.

extensor digitorum longus (EDL) muscle are shown in Table 1. In this preliminary experiment, we tested all compounds in the racemic form at 100 μM concentration, a value close to the concentration required (80 μM) to produce a gCl 50% block from 2-(4-chlorophenoxy)propanoic acid (**2**), one of the most potent modulators of chloride conductance in skeletal muscle fibres. All of them showed a reduced potency in blocking gCl in comparison to racemic **2**, but the different blocking activity related to each compound suggests that the length of the aliphatic chain markedly affects the gCl block. In particular, compounds **4a** and **4b**, having one or two methylenic groups on the side-chain, were poorly effective producing only a 13 and 25% decrease of gCl, respectively. Compound **4c** was the most effective derivative in this series, producing a 46% block of gCl. A further increase in the distance of the phenoxy group from the stereogenic centre led, again, to a reduced potency. In fact, compounds **4d** and **4e**, having one or two additional methylenic groups with respect to compound **4c**, were less effective, both molecules producing only a 30% decrease of gCl.

We also investigated the activity of compound **4f**, which differs from **4c** only for the presence of a methoxy group in place of chlorine on the aromatic ring of the side-chain. The choice of this substituent has been made because of its different electronic effects, the methoxy group being a strong electron donor which contributes to make the benzene ring electron-rich. The resulting effect on chloride conductance, however, was similar to that of the related **4c**, producing a 48% reduction of gCl.

These results indicate that compounds **4a**–**f** have a reduced blocking activity on chloride ion flux of skeletal muscle membrane as compared with **2**. A reasonable explanation for this could be given in terms of steric effects, that is, the aryloxyalkyl group bound to the stereogenic centre, would be too bulky to interact properly with a receptor site where, probably, an hydrophobic pocket of limited size is present. Moreover, the molecules of these acids could approach differently to the receptor, as the phenoxy group of the side-chain is able to mimic the aryloxy moiety α to the carboxylic function. This alternative binding, however, would increase the distance between the phenoxy and the carboxylic groups, while interacting with the corresponding receptor sites, as a consequence of the presence of the intermediate methylenic chain and this would be detrimental for the activity. In previous studies, in fact, we reported that this distance is pivotal for the pharmacological activity of this class of compounds [15].

On the other hand, in this series of compounds, the blocking activity is increased by lengthening the alkyl chain up to three methylenic groups, then decreases to remain constant in the next analogues of the series. It is possible that the molecules of acids **4c** and **4f**, when correctly oriented, are able to assume a conformation in which the alkyl chain is folded in such a way that an appropriate interaction with the hydrophobic pocket occurs while placing the bulky phenoxy group far away from it. Compounds **4a** and **4b** bind more weakly to the receptor because the shorter alkyl chain would keep the phenoxy group still too close to the pocket, whereas in **4d** and **4e** the alkyl chain would be too long to allow as

Table 1
Effect of *in vitro* application of clofibric acid analogues **4a**–**f** on gCl of rat skeletal muscle

Experimental condition	Dose (μM)	Number of fibres	gCl (μS/cm^2)	% Reduction of gCl
Control		63	2759 ± 69	
2	100	20	1159 ± 113 [a]	58 ± 3.7
4a	100	28	2413 ± 99 [a]	13 ± 3.0
4b	100	19	2060 ± 101 [a]	25 ± 2.9
4c	100	37	1493 ± 102 [a]	46 ± 3.4
4d	100	16	1847 ± 86 [a]	33 ± 2.5
4e	100	39	1883 ± 91 [a]	32 ± 2.9
4f	100	21	1420 ± 79 [a]	48 ± 2.4

gCl, resting chloride conductance of skeletal muscle fibres. All tested compounds did not show any effect on the potassium conductance (gK), nor produced remarkable modifications of the resting membrane potential of the examined fibres. The values of gK measured in normal solution and after application of **4c** (one of the most potent compounds) were 319 ± 60 and 323 ± 51 μS/cm^2, respectively.

[a] Significantly different with respect to control value, $P < 0.005$ or less.

an appropriate interaction as **4c**. This hypothesis is confirmed from the same activity of compounds **4c** and **4f**; in these derivatives, in fact, the different substituent (Cl or CH_3O) on the aryloxy moiety of the side-chain, being in a part of the molecule not involved in the binding, would not affect the interaction with the receptor.

The preparation of the enantiomers of the more active derivatives is in progress and their pharmacological activity will be reported separately.

4. Experimental

Column chromatography was performed on ICN silica gel 60 Å (63–200 μm) as the stationary phase. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Mass spectra were recorded with a HP GC-MS 6890-5973 MSD spectrometer, electron impact 70 eV, equipped with HP chemstation. Infrared and ^{1}H NMR spectra were recorded on a FT-IR spectrophotometer Perkin–Elmer, Spectrum one, and a Bruker AM 300 WB (300 MHz) spectrometer, respectively. Microanalyses were carried out with a Carlo Erba mod. 1106 analyzer (the analytical results are within $\pm 0.4\%$ of theoretical values).

*4.1. 2,3-Bis(4-chloro-phenoxy)propanoic acid (**4a**)*

A solution of NaOH (0.54 g, 13.4 mmol) in 1.5 ml of water was added to a mixture of ethyl 2,3-dibromopropanoate (1.00 g, 3.73 mmol) and 4-chlorophenol (1.24 g, 9.7 mmol) at 40 °C. The mixture was refluxed with stirring for 3 h, treated with 1 ml of conc. HCl at room temperature (r.t.) and extracted with chloroform. The organic layer was dried over sodium sulfate and the solvent removed under reduced pressure to give 1.5 g of a yellow solid which was crystallized from chloroform–hexane. White crystals, m.p.: 128–129 °C (0.98 g, yield: 80%).

IR (KBr): 1718 cm^{-1} (C=O). MS (methylester), m/z (rel. abund.): 340 (M^+, 100). ^{1}H NMR ($CDCl_3$): δ 7.27–7.20 (m, 4H, aromatic); 6.90–6.82 (m, 4H, aromatic); 5.48 (bs, 1H, exchange with D_2O, COOH); 4.98 (t, 1H, CH); 4.42 (d, 2H, CH_2). *Anal.* ($C_{15}H_{12}Cl_2O_4$) C,H.

*4.2. Diethyl 2-(4-chloro-phenoxy)malonate (**5**)*

A mixture of chloromalonic acid diethyl ester (3.72 g, 19.1 mmol) and sodium 4-chlorophenate (3.02 g, 20.1 mmol), prepared from an equivalent amount of 4-chlorophenol and sodium in absolute ethanol, was stirred and heated under reflux in acetone (100 ml) for 3.5 h. The solvent was removed under reduced pressure, the residue was taken up with water and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over sodium sulfate and concentrated to give 5.9 g of a crude oil which was purified by column chromatography on silica gel eluting with a 9:1 mixture of petroleum ether/ethyl acetate. Pale yellow waxy solid (4.2 g, 77%).

MS, m/z (rel. abund.): 286 (M^+, 100), 141 (89). ^{1}H NMR ($CDCl_3$): δ 7.26–6.80 (m, 4H, aromatic); 5.14 (s, 1H, CH); 4.30 (q, 4H, $2CH_2$); 1.29 (t, 6H, $2CH_3$).

*4.3. General procedure for the preparation of aryloxyalkylbromides (**6b–f**)*

A 1.6 N NaOH solution (11 mmol, 7 ml) was added dropwise, during 45 min, to a stirred boiling suspension of the suitable phenol (10 mmol) and alkyldibromide (13 mmol) in water (20 ml). The mixture was heated under reflux for 4 h. After cooling, it was taken up with chloroform and the aqueous layer was separated. The organic layer was washed with 2 N NaOH and brine, dried over sodium sulfate and evaporated under reduced pressure. The mixture was purified by column chromatography on silica gel eluting with petroleum ether.

*4.3.1. 4-Chloro-phenoxyethylbromide (**6b**)*

Yield: 52%; MS, m/z (rel. abund.): 234 (M^+, 6), 107 (100).

*4.3.2. 4-Chloro-phenoxypropylbromide (**6c**)*

Yield: 70%; MS, m/z (rel. abund.): 248 (M^+, 36), 128 (100).

*4.3.3. 4-Chloro-phenoxybutylbromide (**6d**)*

Yield: 49%; MS, m/z (rel. abund.): 262 (M^+, 19), 128 (100).

*4.3.4. 4-Chloro-phenoxypentylbromide (**6e**)*

Yield: 62%; MS, m/z (rel. abund.): 276 (M^+, 18), 128 (100).

*4.3.5. 4-Methoxy-phenoxypropylbromide (**6f**)*

Yield: 67%; MS, m/z (rel. abund.): 244 (M^+, 66), 124 (100).

*4.4. General procedure for the preparation of acids **4b–f***

A solution of **5** (10 mmol) in dry DMF (25 ml) was added dropwise to a suspension of NaH (15 mmol, 95% powder) in dry DMF (20 ml) at 0 °C. After stirring at r.t. for 20 min, a solution of the suitable aryloxyalkylbromide **6** (11.5 mmol) in dry DMF (15 ml) was added dropwise and the resulting reaction mixture stirred at 55 °C for 20 h. The solvent was removed under reduced pressure and the residue poured into water and ex-

tracted with diethyl ether. The organic layer was washed with saturated ammonium chloride solution, dried over sodium sulfate and the solvent evaporated *in vacuo*. The residue was refluxed under stirring with 1 N NaOH (25 ml) in 95% ethanol (35 ml) for 4 h. The organic solvent was distilled off under reduced pressure and the remaining aqueous phase washed with diethyl ether, acidified to pH 2 with 6 N HCl and extracted with diethyl ether. The combined organic extracts were dried over sodium sulfate and the solvent removed under reduced pressure. The resulting products were heated at 160 °C for 2 h affording the desired acids which were obtained as pure white solids by crystallization from chloroform–hexane.

4.4.1. 2,4-Bis(4-chloro-phenoxy)butanoic acid (**4b**)

Yield: 35%; m.p.: 118–119 °C. IR (KBr): 1729 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 7.26–6.77 (bs, 1H, exchange with D_2O, COOH); 7.26–7.17 (m, 4H, aromatic); 6.87–6.77 (m, 4H, aromatic); 4.91 (dd, 1H, CH); 4.16 (t, 2H, OCH_2); 2.51–2.40 (m, 2H, CH_2CH). MS (methylester), *m*/*z* (rel. abund.): 354 (M^+, 15), 227 (100). *Anal.* ($C_{16}H_{14}Cl_2O_4$) C, H.

4.4.2. 2,5-Bis(4-chloro-phenoxy)pentanoic acid (**4c**)

Yield: 36%; m.p.: 112–114 °C. IR (KBr): 1709 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 7.25–7.17 (m, 4H, aromatic); 6.83–6.73 (m, 4H, aromatic); 5.94–5.78 (bs, 1H, exchange with D_2O, COOH); 4.68 (t, 1H, CH); 3.97 (t, 2H, OCH_2); 2.20–2.13 (m, 2H, CH_2CH); 2.05–1.96 (m, 2H, OCH_2CH_2). MS (methylester), *m*/*z* (rel. abund.): 368 (M^+, 20), 241 (100). *Anal.* ($C_{17}H_{16}Cl_2O_4$) C, H.

4.4.3. 2,6-Bis(4-chloro-phenoxy)hexanoic acid (**4d**)

Yield: 50%; m.p.: 90–91 °C. IR (KBr): 1722 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 8.20–7.60 (bs, 1H, exchange with D_2O, COOH); 7.26–7.19 (m, 4H, aromatic); 6.84–6.76 (m, 4H, aromatic); 4.63 (t, 1H, CH); 3.94 (t, 2H, OCH_2); 2.06 (q, 2H, CH_2CH); 1.86–1.74 (m, 2H, OCH_2CH_2); 1.74–1.70 (m, 2H, CH_2CH_2CH). MS (methylester), *m*/*z* (rel. abund.): 382 (M^+, 38), 128 (100). *Anal.* ($C_{18}H_{18}Cl_2O_4$) C, H.

4.4.4. 2,7-Bis(4-chloro-phenoxy)heptanoic acid (**4e**)

Yield: 35%; m.p.: 111–112 °C. IR (KBr): 1706 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 7.24–7.17 (m, 4H, aromatic); 6.82–6.74 (m, 4H, aromatic); 5.10–4.52 (bs, 1H, exchange with D_2O, COOH); 4.60 (t, 1H, CH); 3.89 (t, 2H, OCH_2); 2.03–1.96 (m, 2H, CH_2CH); 1.79–1.73 (m, 2H, OCH_2CH_2); 1.60–1.48 (m, 4H, $CH_2CH_2CH_2CH$). MS (methylester), *m*/*z* (rel. abund.): 396 (M^+, 48), 81 (100). *Anal.* ($C_{19}H_{20}Cl_2O_4$) C, H.

4.4.5. 2-(4-Chloro-phenoxy)-5-(4-methoxy-phenoxy)-pentanoic acid (**4f**)

Yield: 35%; m.p.: 119–121 °C. IR (KBr): 1726 cm^{-1} (C=O). ^1H NMR ($CDCl_3$): δ 7.25–7.18 (m, 2H, aromatic); 6.90–6.70 (m, 6H, aromatic); 6.60–5.80 (bs, 1H, exchange with D_2O, COOH); 4.66 (dd, 1H, CH); 3.95 (t, 2H, OCH_2); 3.75 (s, 3H, OCH_3); 2.25–2.10 (m, 2H, CH_2CH); 2.08–1.92 (m, 2H, OCH_2CH_2). MS (methylester), *m*/*z* (rel. abund.): 364 (M^+, 47) 241 (100). *Anal.* ($C_{18}H_{19}ClO_5$) C, H.

4.5. Pharmacology

4.5.1. Methods

The new synthesized compounds have been tested *in vitro* on membrane ionic conductance of EDL muscle of adult male Wistar rats of 350–400 g. The muscle was removed under urethane anaesthesia and placed in a temperature controlled chamber at 30 °C and bathed with a physiological solution or a chloride-free solution in the absence and presence of the tested compounds. The normal physiological solution had the following composition (in mM): 148 NaCl, 4.5 KCl, 2.0 $CaCl_2$, 1.0 $MgCl_2$, 0.44 NaH_2PO_4, 12 $NaHCO_3$, 5.5 glucose. The chloride-free solution was prepared by equimolar replacement of sulfate salts for NaCl and KCl and nitrate salts for $CaCl_2$ and $MgCl_2$. Both solutions were continuously bubbled with 95% O_2 and 5% CO_2 and pH was maintained between 7.2 and 7.3. The total resting ionic conductance of sarcolemma (gm) of muscle fibres was calculated from the cable parameters, and in particular from the membrane resistance (Rm) values, measured by standard cable analysis with the two intracellular microelectrode technique. In brief, a voltage sensitive microelectrode (3 M KCl) was used to measure the membrane potential and the voltage deflection (electrotonic potential), monitored at two distances (0.5 mm and about 1 mm), in response to a hyperpolarizing square wave current pulse passed through a second electrode (2 M potassium citrate). Current pulse generation, acquisition of the voltage records and calculation of membrane resistance were carried out under computer control as detailed elsewhere [11]. In each fibre, the total membrane conductance (gm) was 1/Rm in the normal physiological solution and is due for 70–80% to the chloride conductance (gCl), the remaining being mostly the resting conductance to potassium ions (gK). Aqueous bicarbonate stock solutions of each compound were prepared daily and the final concentrations used were obtained by appropriate dilution with normal physiological solution. Each drug was incubated for at least 20 min before recordings to allow the steady-state drug effect to be reached. The data are expressed as mean $\pm$ SEM [11]. Statistical difference between means was evaluated by Student's test.

Acknowledgements

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