USE OF QSAR IN DESIGN OF ANTIINFLAMMATORY FLUORINATED ARYLALKANOIC ACIDS

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Dedicated to Professor Otto Exner on the occasion of his 65th birthday.

A series of 3-fluoro-4-alkoxyphenylalkanoic acids *III* was synthetized and their antiinflammatory activity and fibrinolytic capacity was evaluated. The suitable fluorinated derivative with better pharmacological profile than 3-chloro-4-benzyloxyphenylacetic acid (benzofenac) was selected. Experimental, biological activities of acids *III* were compared with those calculated by introducing the physico-chemical parameters into the formerly derived regression equations. Good coincidence was found out, as well as similarity of the regression equations derived for the original series of acids extended by the acids *III*. Lipophilicity of the acids under study was evaluated by partition thin-layer chromatography; the values of log *P* of benzyloxy derivatives *IIIc*—*IIIf* were lower than tabulated values — probably due to the intramolecular hydrophobic interactions of aromatic nuclei.

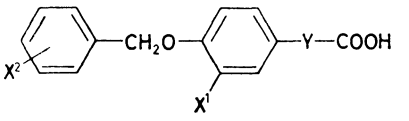
Antiinflammatory activity of arylalkanoic acids was studied using structure–activity relationships, and the results were used for structural optimization. Such an analysis of a series of substituted cinnamic[1] and 2-arylbutanoic acids[2] indicated that more active antiinflammatory acids belonged to a class with higher acidity of the parent structure, probably with shorter connecting chain between aromatic nucleus and carboxyl. The best substitution on the aromatic ring should be a combination of higher alkoxy group and a halogen. The series of substituted benzyloxyarylacetic acids with general formula *IA* was synthetized[3]. The antiinflammatory activity was evaluated in two tests of experimental inflammation and inhibition of kaolin and adjuvant edema was expressed as the activity indices I^K and I^F. Regression analysis led to the equations (*1*) and (*2*). The Eq. (*1*) holds[4] for the series of substituted benzyloxyarylacetic acids *IA*, Eq. (*2*) for the same series extended[5] by alkoxyarylacetic acids *II*.

$$\log I^F = 0{\cdot}67 \sum\pi - 0{\cdot}20 (\sum\pi)^2 + 0{\cdot}52 \sum\sigma - 0{\cdot}53 \qquad (1)$$

$$n = 25\,, \quad r = 0{\cdot}848\,, \quad s = 0{\cdot}101\,, \quad F = 18{\cdot}0$$

$$\log I^{K} = 1{\cdot}167 \sum\pi - 0{\cdot}278 (\sum\pi)^2 + 0{\cdot}289 \sum\sigma - 1{\cdot}237 \qquad (2)$$

$$n = 39\,, \quad r = 0{\cdot}940\,, \quad s = 0{\cdot}071\,, \quad F = 89{\cdot}3$$

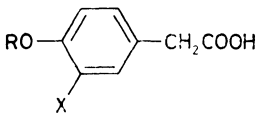


IA–IE

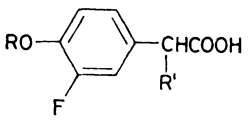
Y = CH_2, $CH(CH_3)$, CH_2CH_2, $CH(CH_3)CH_2$, $CH_2CH(CH_3)$

X^1 = H, Cl, Br, CH_3, CH_3O

X^2 = H, 4-Cl, 4-R, 4-RO, 3-Cl-4-RO, 3-Br-4-R



II X = H, Cl



III

The acids *IA–IE* were also subjected[6] to correlation analysis in an attempt to explain the influence of length of the linking chain Y on the antiinflammatory effect. For inhibition of kaolin edema, Eq. (*3*) was derived in which I_L was an indicator variable characterizing length of the chain Y.

$$\log I^{K} = 1{\cdot}125 (\sum\pi + \Delta\pi) - 0{\cdot}273 (\sum\pi + \Delta\pi)^2 - 0{\cdot}388\, \Delta pK - \\ - 0{\cdot}155 I_L - 1{\cdot}210 \qquad (3)$$

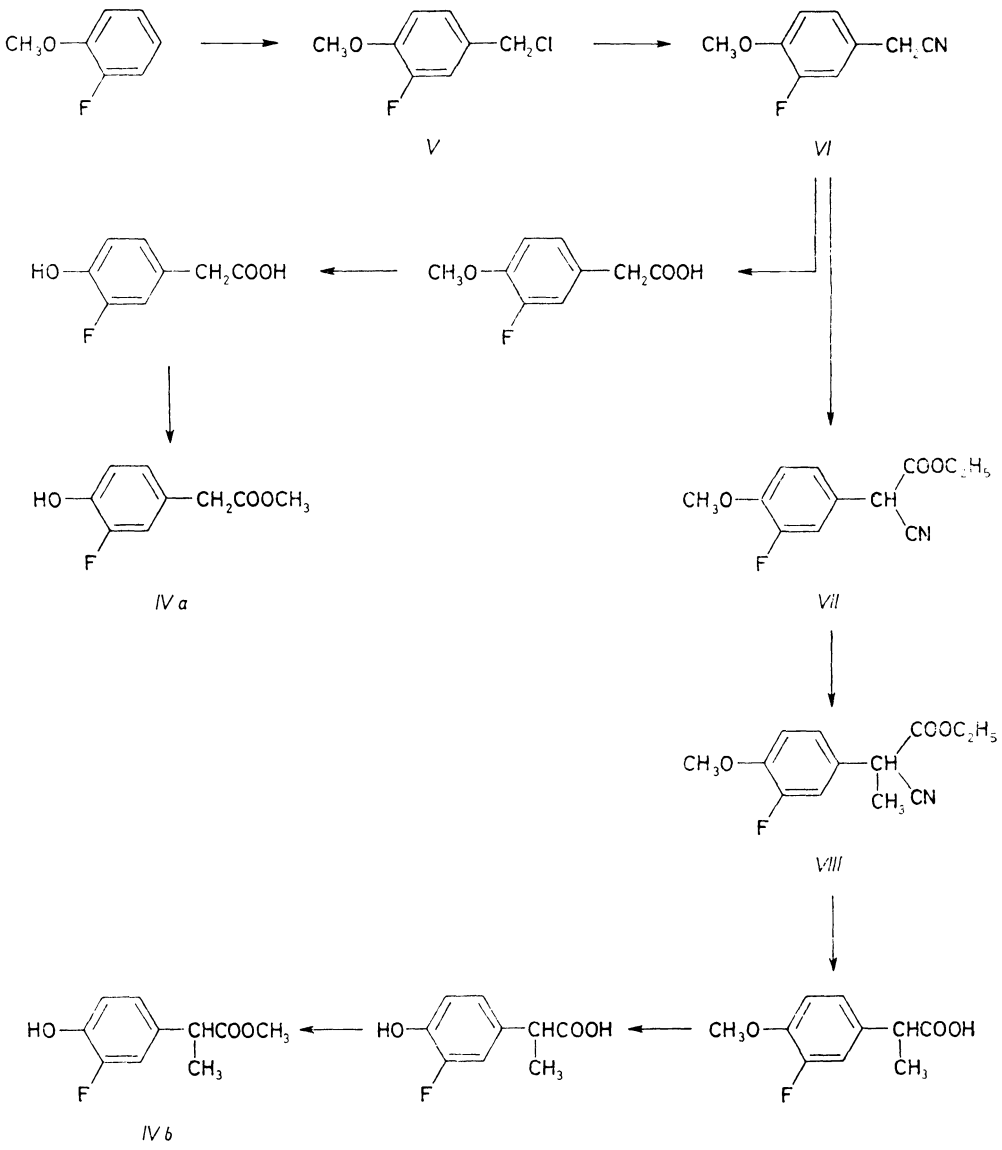
$$n = 50\,, \quad r = 0{\cdot}909\,, \quad s = 0{\cdot}099\,, \quad F = 53{\cdot}7$$

The results of QSAR led to the conclusion that in the series of acids *I* and *II* it was hardly possible to expect more potent derivatives than 3-chloro-4-benzyloxyphenyl acetic acid. This acid with provisional name benzofenac[7,8] was subjected to thorough clinical evaluation. Unfortunately, benzofenac showed irritant effect connected with the anaphylactic reaction on skin. A series of arylacetic and 2-arylpropanoic acids *III* substituted by fluorine on the aromatic nucleus has been prepared to find analogues of benzofenac with better pharmacological profile. The acids *IIIa–IIIf* were prepared by alkylation of methyl esters of corresponding 4-hydroxy derivatives and by subsequent hydrolysis. Methyl esters of 3-fluoro-4-hydroxyphenyl alkanoic acids *IVa*, *IVb* were synthetized from 2-fluoroanisole according to Scheme 1.

A number of antiinflammatory substances of acidic nature increase endogenous fibrinolytic activity[9] in plasma in vitro. In the series of acids *I* and *II* we obtained[10] Eq. (*4*) by the regression analysis of activation of fibrinolysis. Also the fibrinolytic capacity of acids *III* was determined and the experimental values were compared with those calculated from Eq. (*4*).

$$\log (1/C^{F}) = 0{\cdot}615 \sum\pi_{tab} + 0{\cdot}702 \qquad (4)$$

$$n = 35\,, \quad r = 0{\cdot}962\,, \quad s = 0{\cdot}117\,, \quad F = 397$$



SCHEME 1

EXPERIMENTAL

Methods

The ^{1}H NMR spectra of the acids *IIIa*—*IIIf* and esters *IVa* and *IVb* were measured in 6% solution in deuteriochloroform with tetramethylsilane as internal standard on Model BS 487s — 80 MHz

Tesla (Czechoslovakia) spectrometer. Purity of the compounds *III* and *IV* and their intermediates was tested by gas chromatography in Fractovap 2 450 (Carlo Erba, Italy) using a glass column (i.d. 3·5 mm, length 1 m) packed with Gas-Chrom Q 100/120 mesh moistened with 3% OV 17. The acids *III* were derivatized with diazomethane before measuring.

The partition coefficients *P* of the acids *IIIc*, *IIIf* were determined by shake-flask method[11] in a system octanol–0·2M acetate buffer (pH 3·4). The concentrations of both phases were measured spectrophotometrically on a Unicam SP 8000 spectrophotometer, the partition coefficients were calculated as a ratio of concentrations in octanol and aqueous phases. For chromatographic testing of the acids *IIIc*—*IIIf* and of the arylacetic and 2-arylpropanoic acids (Table I), thin layers of silica gel GF_{254} and silanized silica gel (Kieselgel 60, F_{254} silanisiert, Merck, F.R.G.) were used. The plates were impregnated with a 5% solution of silicone oil (Lukoil 100, VChZ Kolín, Czechoslovakia) in diethylether and dried at 20°C for 16 h. The mobile phase was a mixture of acetone and a 0·5M citrate buffer (pH 3·4) in a ratio 1 : 1. For calculation of $\sum\pi$ of the substituents on the aromatic ring, lipophilicity parameters π derived[12] for arylacetic acids were used. The value of $\Delta\pi$ is[6] 0 for arylacetic acids *IIIa*—*IIId* and 0·35 for 2-arylpropanoic acids *IIIe* and *IIIf*. The values of log *P* of acids *IIIc*—*IIIf* were obtained by putting the experimental R_M values to corresponding regression equations (*5*)—(*8*). Equations (*5*) and (*6*) were derived

TABLE I

Chromatography of arylacetic and 2-arylpropanoic acids

$X\text{-}C_6H_4CH(R)CO_2H$

R	X	log *P*[a]	Silica gel (SG)		Silanized SG	
			R_F	R_M	R_F	R_M
H	H	1·45	0·746	−0·47	0·680	−0·33
H	4-Cl	2·15	0·733	−0·435	0·610	−0·19
H	4-C_2H_5	2·43	0·680	−0·33	0·520	−0·03
H	3-Cl-4-$(CH_3)_2CHO$	2·71	0·640	−0·25	0·445	0·095
H	4-$(CH_3)_2CH$	2·85	0·613	−0·195	0·400	0·18
H	4-$(CH_3)_3C$	3·13	0·580	−0·14	0·340	0·29
H	3-Cl-4-$C_6H_5CH_2O$	3·41[b]	0·570	−0·12	0·320	0·33
H	4-$C_5H_{11}O$	3·46	0·500	0	0·305	0·36
H	3-Cl-4-$C_6H_{13}O$	4·41	0·360	0·25	0·140	0·79
CH_3	4-CH_3O	1·81	0·733	−0·435	0·585	−0·15
CH_3	4-Br	2·70	0·670	−0·31	0·460	0·07
CH_3	3-Cl-4l$(CH_3)_2CHO$	3·06	0·640	−0·25	0·325	0·32
CH_3	4-$(CH_3)_2CHCH_2$	3·60	0·570	−0·12	0·190	0·63
CH_3	3-Cl-4-$C_6H_5CH_2O$	3·61[b]	0·500	0	0·200	0·60
CH_3	3-Cl-4-$C_5H_{11}O$	4·26	0·445	0·095	0·130	0·83

[a] Values calculated from logarithms of experimental partition coefficients of phenylacetic (1·45) or 2-phenylpropanoic (1·80) acids and parameters π derived[12] for arylacetic acids; [b] determined experimentally.

for R_M values of arylacetic acids using impregnated silica gel and silanized silica gel, respectively. Similar equations (*7*) and (*8*) were obtained for R_M values of 2-arylpropanoic acids.

$$\log P = 3{\cdot}274R_M + 3{\cdot}554 \qquad (5)$$

$$n = 9\,,\quad r = 0{\cdot}997\,,\quad s = 0{\cdot}067\,,\quad F = 1\,275{\cdot}8$$

$$\log P = 2{\cdot}519R_M + 2{\cdot}455 \qquad (6)$$

$$n = 9\,,\quad r = 0{\cdot}993\,,\quad s = 0{\cdot}107\,,\quad F = 487{\cdot}3$$

$$\log P = 4{\cdot}154R_M + 3{\cdot}881 \qquad (7)$$

$$n = 6\,,\quad r = 0{\cdot}966\,,\quad s = 0{\cdot}247\,,\quad F = 56{\cdot}0$$

$$\log P = 2{\cdot}263R_M + 2{\cdot}308 \qquad (8)$$

$$n = 6\,,\quad r = 0{\cdot}985\,,\quad s = 0{\cdot}163\,,\quad F = 134{\cdot}2$$

The values of pK were calculated from the relationships[13] between pK and Hammett σ derived for arylacetic and 2-arylpropanoic acids.

The regression coefficients were calculated from the experimental data by multiple regression analysis. The statistical significance of all equations was evaluated by the correlation coefficient r, standard deviation s and Fischer–Snedecor criterion F.

Activation of fibrinolysis was assessed by the method of hanging clot[14] prepared in human plasma and suspended in a solution of the compound tested. The activation was expressed as the minimum molar concentration C^F that dissolved the clot after 24 h incubation at 37°C. Inhibition of kaolin edema was assessed by the Hillebrecht method[15] which was described previously[3]. The experimental procedure for determination of adjuvant edema inhibition was described elsewhere[16]. The effect of a compound was expressed in percent of inhibition of inflammation in comparison with the untreated groups, and the activity indices I^K and I^F were calculated as a ratio of the effects of the tested compound and ibuprofen as a standard.

Methyl 3-fluoro-4-hydroxyphenylacetate (*IVa*)

2-Fluoroanisole (37·8 g, 0·3 mol) was added to the suspension of zinc chloride (3·4 g) and paraformaldehyde (19·0 g) in 145 ml of acetic acid. The mixture was heated to 40°C and hydrogen chloride was introduced into the solution until the mass increased by 27·3 g. After heating and mixing for 8 h, the mixture was diluted by 100 ml of water and 140 ml of toluene. Extraction by 65 ml of toluene was repeated twice. The combined extracts were washed by 2M-NaOH and by saturated solution of calcium chloride. On evaporation of the solvent, the yield was 57·8 g (84%) of crude 3-fluoro-4-methoxybenzyl chloride (*V*, purity 84·9% according to GLC). The crude *V* (57·6 g) was diluted by 30 ml of dimethylsulfoxide and added to a suspension of 19·7 g (0·3 mol) of sodium cyanide in 100 ml of dimethylsulfoxide at 40°C. After stirring for 3 h at 40—45°C, the solution was poured into 400 ml of ice water. The precipitate was filtered off and washed by water. On drying, 42·0 g (90%) of 3-fluoro-4-methoxyphenylacetonitrile (*VI*) was obtained m.p. 36—40°C. The nitrile *VI* (41·9 g) was heated for 5 h with a solution of 32 g of potassium hydroxide in 120 ml of ethanol and 30 ml of water. After distillation of ethanol, the residue was diluted by water to a volume of 175 ml. The solution was filtered over the charcoal and the filtrate was acidified by 50% H_2SO_4. Resulting 3-fluoro-4-methoxyphenylacetic acid was filtered and dried, yield 45·0 g (96%), m.p. 110—115°C. The product was dissolved in 600 ml of boiling toluene, 100 ml toluene was distilled off and 42·8 g of aluminium chloride was added at tempera-

ture not exceeding 25°C. The mixture was then boiled for 5 h and 260 ml of 10% HCl was added to the cooled solution. The precipitate was filtered off, the filtrate was extracted twice by 75 ml of 1,2-dichloroethane and combined extracts were washed successively by 5% NaOH and water. The alkaline solution was combined with the precipitate and after adjusting pH to 12 by 5% NaOH, it was filtered over the charcoal and the filtrate was acidified by 50% H_2SO_4. The oil was extracted into ether and the extracts were evaporated after drying. The yield was 27·8 g (67%) of 3-fluoro-4-hydroxyphenylacetic acid m.p. 109—111°C. The acid (27·7 g) was esterified by boiling with 150 ml of methanol containing 3·0 g of hydrogen chloride for 6 h. After evaporation of methanol, the oil was diluted by 75 ml of 1,2-dichloroethane and washed with water. The solvent was evaporated and the rest was distilled; the fraction with b.p. 90—93°C/13·3 Pa was collected and 25·0 g (84%) of methyl 3-fluoro-4-hydroxyphenilacetate (*IVa*, purity 99·5% according to GLC; calculated 10·32% F, found 10·18% F).

Methyl 2-(3-fluoro-4-hydroxyphenyl)propionate *IVb*

The solution of sodium ethoxide (prepared from 6·4 g of sodium and 155 ml of ethanol) was added at 95—100°C to the mixture of 42·0 g of nitrile *VI* (0·25 mol) and 200 ml of diethyl carbonate. The mixture was heated and ethanol was distilled off. The temperature of the distillate increased up to 125°C. The solid distillation residue was dissolved in the mixture of 25 ml of acetic acid and 100 ml of water and stirred for 2 h at 20°C. The solution was then extracted twice by 125 ml of toluene and the extracts were washed by water, dried and concentrated in vacuo. The rest was distilled and the fraction with b.p. 140—143°C/13·3 Pa yielded 46·2 g of ester *VII* (purity 92·5% according to GLC). A solution of *VII* (46·0 g) in 70 ml of ethanol was slowly added to a solution of sodium ethoxide (from 4·2 g of sodium in 145 ml of ethanol). The suspension thus produced was mixed with 51·7 g (0·36 mol) of methyl iodide at 20°C. After heating to 40°C for 3 h and boiling for 3 h, ethanol was distilled and 130 ml of water was added to the residue. The separated oil was extracted by toluene and after drying and evaporation of solvent, the product was isolated by distillation. The yield was 39·8 g (purity 94% according to GLC, 32% of theory) of ethyl 2-cyano-2-(3-fluoro-4-methoxyphenyl) propionate *VIII* with b.p. 136 to 138°C/13·3 Pa. It was then hydrolyzed by boiling for 10 h in a solution of 32·0 g potassium hydroxide in 60 ml of ethanol and 160 ml of water. Ethanol was evaporated and the residue was diluted by water to a total volume of 800 ml. The turbid solution was heated to 60°C and filtered. The filtrate was acidified by 50% H_2SO_4 at 50°C and the separated oil was extracted at 20°C by toluene. After evaporation of toluene, 28·7 g of crude 2-(3-fluoro-4-methoxyphenyl)propanoic acid was obtained. The acid (28·5 g) was demethylated a similar way as in the synthesis of *IVa* yielding 2-(3-fluoro-4-hydroxyphenyl)propanoic acid (22·4 g of oil with 95·6% purity according to GLC) which was esterified by boiling in methanolic hydrogen chloride affording 17·2 g (73·5%) of methyl 2-(3-fluoro-4-hydroxyphenyl)propionate (*IVb*, purity 99·0% according to GLC; calculated 9·59% F, found 9·46% F) with b.p. 118—120°C/13·3 Pa.

3-Fluoro-4-alkoxyphenylalkanoic acids *III*

A solution of 0·05 mol of ester *IVa* and *IVb* in 20 ml of methanol was mixed with a solution of sodium methoxide in methanol (prepared from 1·5 g of sodium and 50 ml of methanol). The mixture was stirred for 15 minutes at 20°C, methanol was evaporated and the rest was dissolved in 50 ml of dimethylsulfoxide. The respective alkyl halide (0·075 mol) dissolved in 10 ml of dimethylsulfoxide was added and the mixture was heated to 100°C for 6 h. On cooling down 400 ml of water was added and the separated oil was extracted by ether. The extract was washed by 5% NaOH and by water. After drying and evaporation of the solvent, the crude methyl ester

of 3-fluoro-4-alkoxyphenyl alkanoic acid was obtained. The oil was then hydrolyzed by boiling in a solution of 17·5 g of potassium hydroxide in 17·5 ml of water and 105 ml of ethanol for 8 h. On evaporation of ethanol, 100 ml of water was added and the solution was filtered over the charcoal. The filtrate was acidified by 50% H_2SO_4 and the precipitate of the crude product was crystallized from methanol–water (Table II).

RESULTS AND DISCUSSION

The large differences between experimental ($\log P_{exp}$) and calculated ($\log P_{tab}$) values of partition coefficients for benzyloxy derivatives *IIIc* and *IIIe* were observed (cf. Table III). A decrease in lipophilicity in comparison with expected tabulated values corresponded to analogous results[17] in a group of arylalkoxyarylalkanoic acids. It is probably a consequence of intramolecular hydrophobic interaction of aromatic nuclei of the basic skeleton and the benzyl group. The same conclusion holds for the values of $\log P_{chr}$ obtained from partition chromatography in two systems differing in a type of the stationary phase. The values of $\log P_{chr}$ agree well with $\log P_{exp}$ (cf. Table III). Lipophilicity of the acids *IIIc*–*IIIf* in the regression analysis of their antiinflammatory activity was approximated as the mean value

TABLE II
Characterization of acids *III*

Compound	R′	R	Yield[a] %	M.p., °C (CH_3OH–H_2O)	Formula (M.w.)	Calculated/Found		
						% C	% H	% F
IIIa	H	$(CH_3)_2CHCH_2$	46	88–89·5 (1 : 1)	$C_{12}H_{15}FO_3$ (226·2)	63·70 63·73	6·68 6·63	8·40 8·45
IIIb	H	C_5H_{11}	89	93–95 (1 : 1)	$C_{13}H_{17}FO_3$ (240·3)	64·98 64·72	7·13 7·16	7·91 7·69
IIIc	H	$C_6H_5CH_2$	83	123–124 (2 : 1)	$C_{15}H_{13}FO_3$ (260·3)	69·22 69·45	5·04 5·08	7·30 7·19
IIId	H	4-$ClC_6H_4CH_2$	91	137–138·5 (3 : 1)	$C_{15}H_{12}ClFO_3$ (294·7)	61·13 60·99	4·10 4·01	6·45[b] 6·60
IIIe	CH_3	$C_6H_5CH_2$	56	89–92 (2 : 1)	$C_{16}H_{15}FO_3$ (274·3)	70·06 69·85	5·51 5·46	6·93 6·83
IIIf	CH_3	4-$ClC_6H_3CH_2$	58	110–111·5 (2 : 1)	$C_{16}H_{14}ClFO_3$ (308·7)	62·24 62·09	4·59 4·62	6·15[c] 6·07

[a] Total yield (related to esters *IVa*, *IVb*, respectively) of etherification and hydrolysis; [b] calculated: 12·03% Cl, found: 12·13% Cl; [c] calculated: 11·49% Cl; found: 11·50% Cl.

from both chromatographic determinations (cf. Table IV). However, these values could not be used in QSAR analysis of fibrinolytic capacity. This was already noticed in evaluation of relationships between fibrinolytic capacity and lipophilicity in a series of arylacetic acids, including benzyloxy derivatives. In the regression equation (*4*), the tabulated values of parameters π for characterization of lipophilicity of benzyloxyderivatives gave better results than experimental values. It was necessary to use the tabulated values $\log P_{tab}$ also for acids *IIIc–IIIf* for calculation of fibrinolytic capacity by substituting into Eq. (*4*). The calculated values $\log (1/C^F)_c$ were in a good agreement with the experimental values $\log (1/C^F)_{exp}$ (cf. Table IV). Validity of the formerly derived Eq. (*4*) was supported by Eq. (*9*) which was derived for the original series of acids extended by fluoro derivatives *IIIb–IIIf*

$$\log (1/C^F) = 0{\cdot}584 \sum \pi_{tab} + 0{\cdot}761 \qquad (9)$$

$$n = 40\,, \quad r = 0{\cdot}947\,, \quad s = 0{\cdot}133\,, \quad F = 328$$

The attention was focused on the antiinflammatory activity of the acids studied. We have started from the hypothesis that a decrease in the undesirable side effects might be expected on passing from the arylacetic to 2-arylpropanoic acids. For example, the undesirable effects of 4-isobutylphenylacetic acid were minimized in 2-(4-isobutylphenyl)propanoic acid[18] (ibuprofen). To keep the optimum lipophilicity, it is necessary to compensate its increase in 2-arylpropanoic acids by replacing chlorine in position 3 of acids *IA* (X^1 = Cl) or *II* (X = Cl) by fluorine. The physico-chemical properties and experimental antiinflammatory activities of acids *IIIa–IIIf* are summarized in Table IV. The corresponding values of $\log I_c^K$ and $\log I_c^F$ were

TABLE III
Lipophilicity of acids *IIIc–IIIf*

Compound	$\log P_{tab}$ [a]	$\log P_{exp}$	Silica gel (SG)				Silanized SG			
			R_F	R_M	$\log P_{chr}$	$\sum\pi$	R_F	R_M	$\log P_{chr}$	$\sum\pi$
IIIc	3·49	2·84	0·613	−0·195	2·91[b]	1·46	0·385	0·20	2·96[c]	1·51
IIId	4·35	—	0·560	−0·01	3·52[b]	2·07	0·300	0·37	3·39[c]	1·94
IIIe	3·84	3·25	0·590	−0·16	3·22[d]	1·42	0·293	0·385	3·18[e]	1·38
IIIf	4·70	—	0·560	−0·01	3·84[d]	2·04	0·167	0·70	3·89[e]	2·09

[a] Following values were used for calculations of $\log P_{tab}$: $\log P$ (phenylacetic acid) 1·45, $\log P$ (2-phenylpropanoic acid) 1·80, $\pi(CH_3O) = 0{\cdot}01$, $\pi(C_6H_5) = 1{\cdot}89$, $\pi(F) = 0{\cdot}14$, $\pi(Cl) = 0{\cdot}86$; [b] calculated from Eq. (*5*); [c] calculated from Eq. (*6*); [d] calculated from Eq. (*7*); [e] calculated from Eq. (*8*).

TABLE IV

Biological activities and physico-chemical properties of acids *III*

Compound	log P_{chr}	$(\sum\pi + \Delta\pi)_{chr}$ [a] $(\sum\pi + \Delta\pi)_{tab}$ [b]	$\sum\sigma$	pK ΔpK	C^F (mol l^{-1})	log $(1/C^F)_{exp}$ log $(1/C^F)_c$ [c]	I^K	log I^K_{exp} log I^K_c	I^F	log I^F_{exp} log I^F_c
IIIa	2·90	— 1·45	−0·02	6·77 −0·01	—	—	0·74	−0·131 −0·137[d]	—	—
IIIb	3·60	— 2·15	−0·01	6·76 −0·02	0·009	2·046 2·024	0·78	−0·108 −0·016[d]	—	—
IIIc	2·93	1·48 2·04	−0·05	6·79 0·01	0·008	2·097 1·957	0·66	−0·180 −0·133[e]	1·00	0 −0·002[f]
IIId	3·46	2·01 2·90	−0·05	6·79 0·01	0·007	2·155 2·172	0·87	−0·060 −0·032[e]	0·89	−0·049 −0·026[f]
IIIe	3·20	1·75 2·39	−0·05	6·86 0·08	0·004	2·398 2·485	1·02	0·008 −0·090[e]	1·12	0·049 0·008[f]
IIIf	3·86	2·41 3·25	−0·05	6·86 0·08	0·003	2·523 2·701	0·74	−0·131 −0·086[e]	1·08	0·033 −0·099[f]
Benzo-fenac[g]	3·27	1·82 2·36	−0·02	6·78 0	0·005	2·301 2·154	1·18	0·072 −0·062[e]	1·35	0·130 0·007[f]

[a] Values were calculated as a difference log P_{chr} − 1·45 (i.e. log P of phenylacetic acid); [b] calculated as a sum of parameters π of substituents and $\Delta\pi$ (for *IIIa*—*IIId* 0, for *IIIe* and *IIIf* 0·35); [c] calculated from Eq. (*4*); [d] calculated from Eq. (*2*); [e] calculated from Eq. (3); [f] calculated from Eq. (*1*); [g] 3-chloro-4-benzyloxyphenylacetic acid.

calculated from formerly derived equations (*1*)–(*3*). The high predictive value of these equations is apparent from the closeness of calculated and experimental values of antiinflammatory activity. This is also confirmed by the results of regression analysis in a series of acids extended by the new derivatives *IIIa*–*IIIf*. Equation (*10*) was derived for the inhibition of adjuvant edema in a series of substituted benzyloxyarylacetic acids expanded by the acids *IIIc*–*IIIf*.

$$\log I^{F} = 0{\cdot}76 \sum\pi - 0{\cdot}22 (\sum\pi)^2 + 0{\cdot}53 \sum\sigma - 0{\cdot}61 \qquad (10)$$

$$n = 29\,, \quad r = 0{\cdot}873\,, \quad s = 0{\cdot}096\,, \quad F = 27$$

Equations (*1*) and (*10*) have similar values of the regression coefficients and statistical significance.

Analogously, extension of the original series of aryacetic acids by compounds *IIIa*–*IIId* led to the Eq. (*11*), comparable with Eq. (*2*), derived for the inhibition of kaolin edema.

$$\log I^{K} = 1{\cdot}150 \sum\pi - 0{\cdot}272 (\sum\pi)^2 + 0{\cdot}203 \sum\sigma - 1{\cdot}255 \qquad (11)$$

$$n = 43\,, \quad r = 0{\cdot}921\,, \quad s = 0{\cdot}078\,, \quad F = 73$$

Similarly, the Eq. (*12*) was obtained for a series of benzyloxyarylalkanoic acids extended by the compounds *IIIc*–*IIIf*. This equation corresponds to the original equation (*3*).

$$\log I^{K} = 1{\cdot}149 (\sum\pi + \Delta\pi) - 0{\cdot}278 (\sum\pi + \Delta\pi)^2 - 0{\cdot}315\, \Delta pK - 0{\cdot}155 I_L - 1{\cdot}226 \qquad (12)$$

$$n = 54\,, \quad r = 0{\cdot}916\,, \quad s = 0{\cdot}096\,, \quad F = 64$$

The acid *IIIe*, i.e. 2-(2-fluoro-4-benzyloxyphenyl)propanoic acid, was selected as a suitable candidate for replacement of benzofenac and it was subjected to the extended preclinical trials.

The elemental analyses were carried out in the Department of Microanalysis of the Institute for Pharmacy and Biochemistry (Dr J. Dohnal, Head).

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