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Original article

Antileukotrienic phenethylamido derivatives of arylalkanoic acids in the treatment of ulcerative colitis

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Abstract

A series of arylalkanoic acid derivatives bearing methyl(phenethyl)amino groups were prepared and their inhibition of LTB_4 biosynthesis was evaluated. Regression analysis showed the slightly different parabolic dependences of this activity on lipophilicity of α-methyl and α-unsubstituted alkanoic acid derivatives. The relationship derived for α-unsubstituted alkanoic acids was extended by previously prepared group of similar derivatives of arylacetic acids without any change of regression coefficients and statistical criteria. It was concluded that the most active compounds belong to 2-arylpropanoic acid derivatives with lipophilicity close to log P_{opt} (=6.97). But generally, the structural changes in the acidic part of compounds under study did not yield the substantial improvement of LTB_4 biosynthesis inhibition in comparison with the previously prepared series of derivatives **IV**. The anti-inflammatory effect of the compounds under study was evaluated in three animal models of inflammation and their possible utilization in the treatment of ulcerative colitis (UC) was followed. From 12 evaluated compounds, 4 compounds are more active in UC inhibition than the standard sulfasalazine but it can be stated that the change of connecting chain between aromatic ring and carboxyl did not bring about the important improvement of this activity in comparison with previous derivatives of arylacetic acids. Possible relation between LTB_4 biosynthesis inhibition and ulcerative colitis is seriously broken by the compound **8a** with carbonyl as the additional functional group on the connecting chain between carboxyl and aromatic ring.

Keywords: *N*-Phenethyl-2-arylacetamides; Antileukotrienic activity; QSAR; Regression analysis; Lipophilicity; Treatment of ulcerative colitis

1. Introduction

The ethiology of inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease is still far from full elucidation, but our understanding of the mechanisms underlying intestinal inflammation has increased dramatically during the last 10 years [1–3]. There is an evidence of the activation of mucosal immune system [4] with the final common step realized by the local influx of monocytes, macrophages and polymorphonuclear neutrophils. The processes accounted for the recruitment of these cells include cytokine generation, complement activation and eicosanoid (prostaglandins and leukotrienes) biosynthesis [1,5]. An increased production of platelet-activating factor, high levels of proinflammatory leukotrienes (LT), in particular LTB_4, is characteristic of various immune and inflammatory diseases including IBD [5–7].

LTB_4 is a potent proinflammatory mediator, which plays a significant role in the amplification of many other inflammatory diseases [8,9] including psoriasis, gout, rheumatoid arthritis and asthma. In addition, LTB_4 is a mediator of

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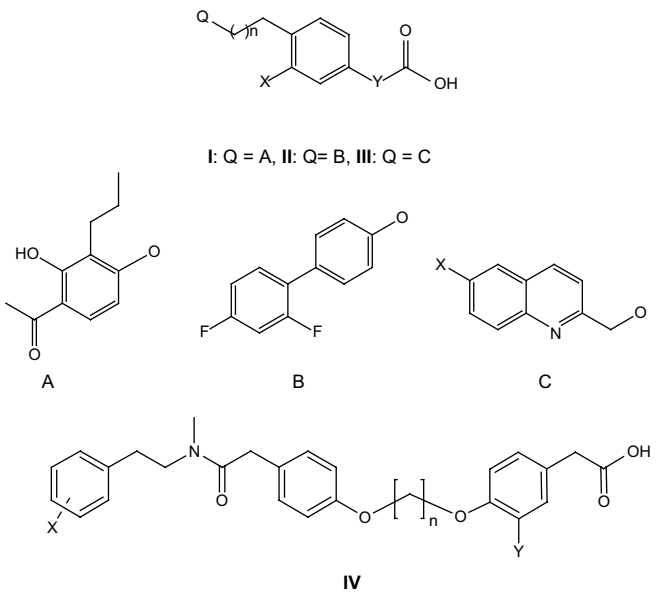
inflammatory pain [10] and binds to peroxisome proliferator-activated receptor (PPARα), which could affect the duration of an inflammatory response to LTB_4 [11]. The positive effect of the decrease of LTB_4 level in colonic mucosa on the course of UC was observed during the treatment of that by the various antileukotrienics. The use of eicosapentenoic acid [12] led to the decrease of LTB_4 level accompanied by the maintenance of remission in children with UC. Also, for antileukotrienic boswellic acids, the promising results were observed [13] in clinical trials of the treatment of rheumatoid arthritis, ulcerative colitis, Crohn's disease and bronchial asthma. The potential therapeutic effect of low-density sodium alginate was studied [14] in a rat model of UC induced by intracolonic administration of acetic acid. The results showed the reduction of colonic damage score and colonic mucosal TNF-α, LTB_4 and PGE_2 levels in treated groups compared with untreated controls. In contrast, the opposite observations are also described in some studies. The investigation [15] whether de novo synthesis of 5-lipoxygenase (5-LO) and consequently the concentration of LTB_4 increased in patients with quiescent IBD led to the conclusion that there is no evidence for this affirmation. Similar conclusion [16] was achieved from the results of multicenter trial of a leukotriene biosynthesis inhibitor MK-591 in the treatment of UC. These controversial results inspired us to evaluate several of our original antileukotrienic compounds in the model of UC. Our first attempt was made [17] with the selected antileukotrienics **I**–**III** originally synthesized as effective antiasthmatics [18,19]. The promising results led to the synthesis of the new series of antileukotrienic substituted arylalkanoic acids bearing phenethylamino moiety. These compounds were preferentially examined for the treatment of UC. The antileukotrienics with lipophilic phenethylamino [16,20–22] or *N*-methylphenethylamino [23] fragment are frequently studied. The present work represents the continuation of our previous contribution [24] concerning phenethylamino derivatives of arylacetic acids (**IV**) with a broad spectrum of antileukotrienic activities. Eq. (1), characterizing the relationship between inhibition of LTB_4 biosynthesis and log *P* values, was derived for the series of compounds **IV**. The number of compounds in correlation is *n*; *r*, *s*, and *F* are statistical criteria, IC_{50} is the molar concentration of the compound causing 50% inhibition (cf. Section 5).

$$\log(1/IC_{50}) = 5.936(\pm 5.627)\log P - 0.476(\pm 0.471)(\log P)^2 - 13.549 \quad (1)$$
$$n = 9,\ r = 0.954,\ s = 0.068,\ F = 41.1$$

The utilization of HPLC characteristics for the evaluation of lipophilicity of compounds **IV** was also studied and Eqs. (2) and (3), expressing the relationship between chromatographic quantities and log *P* values, were derived. Eq. (3) indicates the different influence of polar effects (characterized by σ_1 constants of substituents X and indicator varible I_{NH} for *N*-desmethyl derivatives) on the separation in chromatographic and octan-1-ol/water system, respectively. Log *P*'s



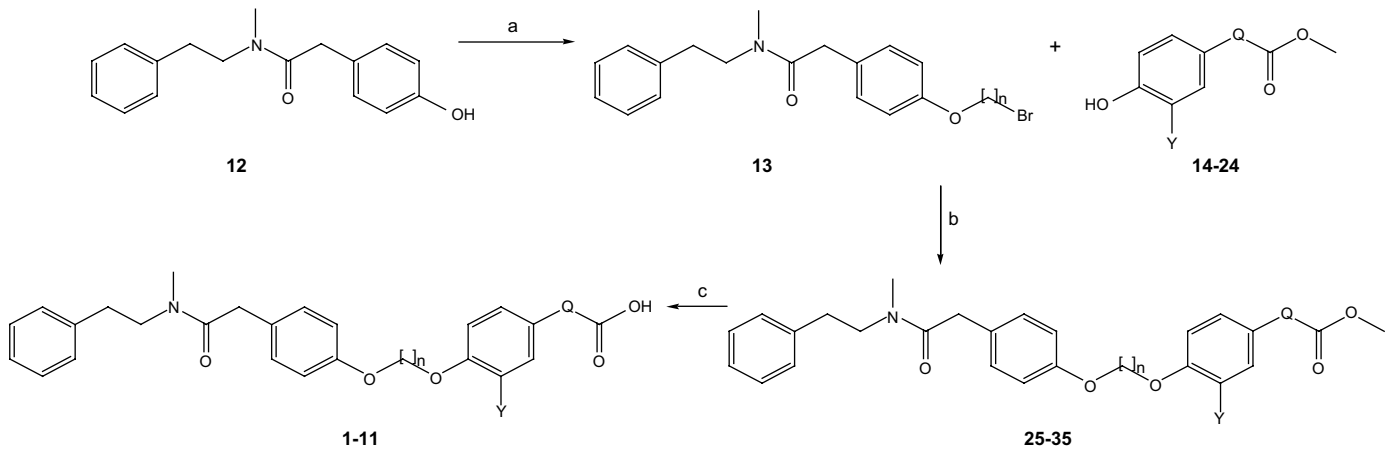
are the calculated values of the logarithms of partition coefficients in the octan-1-ol/water system and *k* represents the capacity factors in HPLC system. Our continuous effort was focused on the elucidation of the role of lipophilicity in the inhibition of LTB_4 biosynthesis using QSAR methodology in the compounds under study.

$$\log k = 0.301(\pm 0.104)\log P + 1.377(\pm 0.596) \quad (2)$$
$$n = 13,\ r = 0.932,\ s = 0.065,\ F = 80.2$$

$$\log k = 0.275(\pm 0.051)\log P + 0.146(\pm 0.076)I_{NH} - 0.252(\pm 0.222)\sigma_1 - 1.344(\pm 0.277) \quad (3)$$
$$n = 13,\ r = 0.987,\ s = 0.028,\ F = 159.0$$

2. Chemistry

The series of compounds **1**–**11** was synthesized using the *N*-methyl-*N*-phenethyl-amino group as the lipophilic part of the molecule and the arylalkanoic acid moiety as the carrier of carboxyl group. The structure of the compounds was modified in the acidic moiety by the different connecting chains between carboxyl and aromatic nuclei, the substitution on the corresponding aromatic ring and by the length of the spacer between both the fragments of the structure. The synthesis of compounds **1**–**11** was carried out according to Scheme 1. The alkylation of esters **14**–**24** by halogenalkoxy derivatives **13a**,**b**,**c** under the conditions of the Williamson reaction [25] gave esters **25**–**35**, which were hydrolyzed to the corresponding acids **1**–**11** (Table 1). The starting amide **12** was prepared identically to Ref. [24] and the methyl esters of 4-hydroxyarylalkanoic acids **14**–**24** were prepared [26,27] from 4-methoxyarylalkanoic acids by *O*-demethylation and subsequent esterification with the exception of

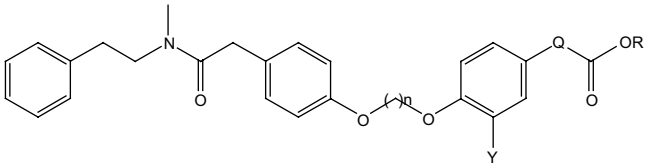


Scheme 1. Synthesis of compounds **1**–**11**: (a) 18-crown-6, K_2CO_3, butan-2-one, 1,3-dibromopropane (1,4-dibromobutane), reflux; (b) K_2CO_3, butan-2-one, reflux; (c) tetrahydrofuran/water 4:1, LiOH, 20 °C.

4-hydroxy-3-methoxy derivatives **17**, **22** and **23**, where the corresponding acids were prepared by special methods.

^{1}H NMR spectra of all compounds including amido group are characterized by splitting of the signals belonging to protons in the vicinity of amido group (cf. Section 5 and Table 4).

Table 1
Characterization of acids **1b**–**11c** and esters **25b**–**35c**



1 - 11 R = H; **25 - 35** R = CH_3

Acids	Esters	Q	Y	*n*
1b	**25b**	$CH(CH_3)$	H	3
1c	**25c**	$CH(CH_3)$	H	4
2b	**26b**	$CH(CH_3)$	Cl	3
2c	**26c**	$CH(CH_3)$	Cl	4
3b	**27b**	CH_2CH_2	H	3
3c	**27c**	CH_2CH_2	H	4
4b	**28b**	CH_2CH_2	CH_3O	3
4c	**28c**	CH_2CH_2	CH_3O	4
5b	**29b**	$CH_2CH(CH_3)$	H	3
5c	**29c**	$CH_2CH(CH_3)$	H	4
6a	**30a**	$CH_2CH_2CH_2$	H	2
6b	**30b**	$CH_2CH_2CH_2$	H	3
6c	**30c**	$CH_2CH_2CH_2$	H	4
7a	**31a**	$CH_2CH_2CH(CH_3)$	H	2
7b	**31b**	$CH_2CH_2CH(CH_3)$	H	3
7c	**31c**	$CH_2CH_2CH(CH_3)$	H	4
8a	**32a**	$COCH_2CH_2$	H	2
9a	**33a**	CH=CH	H	2
9b	**33b**	CH=CH	H	3
9c	**33c**	CH=CH	H	4
10a	**34a**	CH=CH	CH_3O	2
10b	**34b**	CH=CH	CH_3O	3
10c	**34c**	CH=CH	CH_3O	4
11b[a]	**35b**	$CH(CH_3)$	H	3
11c[a]	**35c**	$CH(CH_3)$	H	4

[a] The rest of α-propionic acid is joined to naphthalene ring in position 2, alkoxy group in position 7.

3. Results and discussion

3.1. Biological activities

Compounds **1**–**11** were subjected to evaluation of the inhibition of LTB_4 biosynthesis and the inhibitory activity was expressed by the concentration IC_{50} causing 50% inhibition of LTB_4 biosynthesis. The compounds were also tested for their anti-inflammatory efficiency in two *in vivo* models of inflammation, i.e. carrageenan-induced edema in rats and arachidonic acid-induced ear inflammation in mice. The effects were expressed as percentage inhibition in comparison to untreated control. Selected compounds were subjected to evaluation of anti-inflammatory activity in the *in vivo* model (mice) of UC induced by dextrane disodium sulfate. The efficacy was evaluated clinically (loss of weight, rectal prolapse, blood in stool, stool consistency), pathologically (colonic bleeding, length of colon) and histologically. The results of evaluation of antileukotrienic and anti-inflammatory efficiencies are summarized in Table 2; the values documenting the effect in the model of ulcerative colitis are shown in Table 3. The results of the inhibition of UC proved the higher activity of compounds **2c**, **7c**, **8a**, and **10a** in comparison with the standard sulfasalazine and confirmed our previous statement [24] that the general structure of compounds studied has the potential for the treatment of UC.

3.2. QSAR analysis

3.2.1. Parametrization of lipophilicity

To evaluate total lipophilicity of the compounds studied, the values of log *P*, i.e. logarithms of partition coefficients in the system *n*-octanol–water calculated using the program KOWWIN, Version 1.63, were used. The experimental values determined by reverse phase HPLC and expressed by values of log *k*, where *k* is the capacity factor (cf. Section 5), were also used for the evaluation of lipophilicity of compounds **1**–**11**. The relationship between log *P* values and log *k* values for the series of acids **1**–**11** is expressed by Eq. (4).

Table 2
Antileukotrienic and anti-inflammatory activities of arylalkanoic acid derivatives **1–11**

No.	Log *P*	Log *k*	LTB_4 biosynthesis		Carrageenan edema (% of inhibition)	Ear edema (% of inhibition)	
			IC_{50}[a]	$Log(1/IC_{50})$		A[b]	B[b]
1b[c]	5.58	0.344	100	4.000	9.2	19	3.7 (s)
1c	6.07	0.458	31	4.523	63	19	0
2b[c]	6.22	0.432	9.1	5.041	nd	nd	nd
2c	6.71	0.554	5.6	5.252	44	37	0
3b	6.02	0.324	11	4.959	61	23	3.7 (s)
3c	6.51	0.451	10	5.000	30	13	3.4[e]
4b	5.37	0.175	nd	–	26	12	7.4 (s)
4c	5.86	0.267	8.1	5.092	27	20	11 (s)
5b[c]	6.44	0.502	8.2	5.086	nd	nd	nd
5c	6.93	0.604	10	5.000	37	10	7.4
6a	6.02	0.231	9.5	5.022	36	12	3.6[e]
6b	6.51	0.451	12	4.921	30	13	3.4[e]
6c	7.00	0.600	16	4.796	38	22	3.7[e]
7a	6.44	0.380	19	4.721	14	14	3.7 (s)
7b	6.93	0.636	7.5	5.125	nd	16	3.7[e]
7c	7.42	0.752	10	5.000	56	22	3.7[e]
8a	4.66	−0.089	20	4.699[d]	38	16	3.6[e]
9a	5.31	0.081	47	4.328	43	9.4	3.4[e]
9b	5.81	0.336	8.5	5.071	13	21	3.7 (s)
9c	6.30	0.462	8.7	5.060	20	22	6.7
10a	4.88	−0.061	nd	–	10	23	0
10b	5.37	0.166	nd	–	20	16	7.1[e]
10c	5.86	0.274	13	4.886	5.5 (s)	23	0
11b	6.76	0.617	5.7	5.244	30	12	0
11c	7.25	0.755	5.6	5.252	22	26	3.3[e]

nd: not determined; (s): stimulation.
[a] In μM concentration.
[b] Inhibition of ear lobe edema (A), inhibition of ear lobe hyperemia (B).
[c] Evaluated as cyclohexylammonium salts.
[d] Not included in correlation.
[e] The results are not significant at the level $p < 0.05$ vs. control.

$$\log k = 0.305(\pm 0.052)\log P - 1.490(\pm 0.320) \quad (4)$$
$$n = 25,\ r = 0.966,\ s = 0.058,\ F = 336.4,\ p = 0.005$$

The addition of indicator variable characterizing the presence or absence of α-methyl and/or the polar constants σ of substituents on the aromatic ring of arylalkanoic acids does not improve the correlation. Combining the present series of compounds **1–11** with the previous series [24] of arylacetic acid derivatives **IV** (two NH derivatives were omitted), Eq. (5) was derived. The introduction of σ constants of substituents on phenethylamido aromatic ring did not improve the statistical significance substantially.

$$\log k = 0.294(\pm 0.041)\log P - 1.420(\pm 0.252) \quad (5)$$
$$n = 36,\ r = 0.964,\ s = 0.056,\ F = 456.3,\ p = 0.005$$

3.2.2. Regression analysis of inhibition of LTB_4 biosynthesis

The presence of methyl at α-position to carboxyl significantly affects the inhibition of LTB_4 biosynthesis. Its influence is manifested not only by the slight elevation of activity but also by a transfer of lipophilicity optimum to a higher value. Therefore, the total regression analysis of all compounds under study offered the equation with low statistical significance ($r < 0.7$). Their separation to two groups of arylalkanoic acids differing by the presence and absence of α-methyl is necessary to derive the significant regression equations: Eqs. (6) and (7) for α-unsubstituted and α-methyl derivatives, respectively. The optimum values of lipophilicity, $\log P_{opt}$ are calculated as 6.29 from Eq. (6) and 6.98 from Eq. (7). From Eqs. (6) and (7), the corresponding optimum activities $\log (1/IC_{50})_{opt}$ are calculated as 5.09 and 5.17, respectively.

Table 3
Activities of derivatives of arylalkanoic acids **1–11** in a model of ulcerative colitis

No.	Stool consistence[a]		Rectal prolapse[a]		Intestine bleeding[a]				Length of colon (cm)	Histology
					Small		Large			
	A	B	A	B	A	B	A	B		
1c	100	5/5	0	0/5	20	1/5	100	5/5	7.2 ± 0.5^{b}	$1.4 \pm 0.2^{b,c}$
2c	0	0/5	0	0/5	0	0/5	60	3/5	7.9 ± 0.7	$1.2 \pm 0.8^{b,c}$
3b	80	4/5	0	0/5	0	0/5	100	5/5	$6.8 \pm 0.9^{b,c}$	$2.1 \pm 0.3^{b,c}$
4c	60	3/5	0	0/5	0	0/5	100	5/5	$7.0 \pm 0.3^{b,c}$	$1.7 \pm 0.5^{b,c}$
6a	80	4/5	0	0/5	0	0/5	100	5/5	$7.1 \pm 0.4^{b,c}$	$1.4 \pm 0.4^{b,c}$
6c	60	3/5	0	0/5	0	0/5	100	5/5	7.2 ± 0.6^{b}	1.3 ± 0.5^{c}
7b	100	5/5	0	0/5	0	0/5	60	3/5	$7.2 \pm 0.6^{b,c}$	$1.4 \pm 0.4^{b,c}$
7c	0	0/5	0	0/5	0	0/5	60	3/5	$9.3 \pm 0.5^{b,c}$	$04 \pm 0.3^{b,c}$
8a	0	0/5	0	0/5	0	0/5	20	1/5	9.2 ± 0.6^{b}	0.9 ± 0.0^{c}
10a	40	2/5	0	0/5	0	0/5	40	2/5	7.2 ± 0.3^{b}	1.4 ± 0.5^{c}
10c	80	4/5	0	0/5	0	0/5	100	5/5	$6.8 \pm 0.7^{b,c}$	1.3 ± 0.4^{c}
11c	20	1/5	0	0/5	0	0/5	80	4/5	7.5 ± 0.7	1.2 ± 0.7
Control[d]	100	15/15	7	1/15	13	2/15	100	15/15	7.9 ± 0.5	1.0 ± 0.3
Sulfasalazine	53	8/15	0	0/15	0	0/15	80	12/15	8.1 ± 1.1	0.8 ± 0.3
IV (8b)	0	0/5	0	0/5	0	0/5	0	0/5	$9.1 \pm 0.5^{b,c}$	$0.6 \pm 0.2^{b,c}$
IV (8a)	40	2/5	0	0/5	0	0/5	60	3/5	$8.4 \pm 0.5^{b,c}$	$0.9 \pm 0.2^{b,c}$

[a] A: % of diseased animals, B: the ratio of diseased and total number of animals (used for comparison with similar results in Ref. [24]); the data are expressed as means ± SD at the level of significance <0.05.
[b] Measured vs. control.
[c] Measured vs. sulfasalazine (unpaired two-tailed Student's *t*-test).
[d] DSS in drinking water, 0.5% aqueous solution of (carboxymethyl)cellulose.

$$\log(1/IC_{50}) = 8.657(\pm 6.826)\log P - 0.688(\pm 0.530)(\log P)^2 - 22.144(\pm 20.146) \quad (6)$$
$$n = 10,\ r = 0.877,\ s = 0.108,\ F = 16.0,\ p = 0.005$$

$$\log(1/IC_{50}) = 8.343(\pm 7.284)\log P - 0.597(\pm 0.557)(\log P)^2 - 23.979(\pm 23.706) \quad (7)$$
$$n = 11,\ r = 0.896,\ s = 0.170,\ F = 21.4,\ p = 0.01$$

The extension of the series of α-unsubstituted acids to previously evaluated group of arylacetic acids gives Eq. (8). The statistical significance is slightly better in comparison with Eq. (6); the optimum of lipophilicity is almost the same, $\log P_{opt} = 6.27$. This common dependence on lipophilicity indicates at least the same site of action of both groups of α-unsubstituted acids. The quantity IC_{50} in Eqs. (6)–(8) represents the concentration causing 50% inhibition of biosynthesis of LTB_4.

$$\log(1/IC_{50}) = 6.574(\pm 3.284)\log P - 0.524(\pm 0.274)(\log P)^2 - 15.621(\pm 9.820) \quad (8)$$
$$n = 19,\ r = 0.891,\ s = 0.102,\ F = 36.6,\ p = 0.005$$

The linearized biexponential model [28] was used for the expression of the mentioned biological activity dependence on lipophilicity. The derived equation had no reasonable statistical significance, probably due to asymmetric distribution of experimental data on the axis of lipophilicity. The use of values of $\log k$ determined by HPLC, instead of $\log P$, afforded the regression Eq. (9). The comparison of statistical significance of corresponding equations confirms the previous conclusion [24] that lipophilicity of these compounds is slightly better expressed by $\log P$ values than those of $\log k$.

$$\log(1/IC_{50}) = 5.442(\pm 3.058)\log k - 6.734(\pm 4.501)(\log k)^2 + 3.907(\pm 0.482) \quad (9)$$
$$n = 19,\ r = 0.841,\ s = 0.123,\ F = 22.8,\ p = 0.005$$

4. Conclusions

It can be concluded from the above-mentioned regression relationships that the most active compounds belong to 2-arylpropanoic acids derivatives, i.e. **2c**, **11b**, **11c**, with lipophilicity close to $\log P_{opt}$ (=6.97). But generally, the structural changes in the acidic part of compounds under study did not yield substantial improvement of LTB_4 biosynthesis inhibition in comparison with the previously prepared [24] series of derivatives **IV**. The results of UC inhibition (Table 3) have shown that 4 from 12 evaluated compounds – **2c**, **7c**, **8a**, and **10a** – are more active than the standard sulfasalazine. Two compounds from the previous series of compounds **IV** were included for the sake of comparison. It can be stated that the change of connecting chain between aromatic ring and carboxyl did not bring about important improvement of UC inhibition. We have tried to find some relations among the biological activities studied. It can be stated that the relation between inhibitory activities of LTB_4 biosynthesis and ear lobe edema exists in some qualitative level and the first one is important for ear edema inhibition. Only three compounds, i.e. **7c**, **11c** and **2c** are active in all three activities. Possible relation between LTB_4 biosynthesis inhibition and ulcerative colitis is seriously broken by the compound **8a**. The presence of the next functional group, i.e. carbonyl, and its positive role in the inhibition of UC but not in both the remaining activities is one of the possible explanations. It can be concluded that if the relation between LTB_4 biosynthesis and ulcerative colitis exists, it is probably overlapped by the additional mechanism of this pathological process. Our effort to contribute to the elucidation of these relations and mainly to find compounds with improved inhibitory activity against UC will proceed to the synthesis of arylalkanoic acid derivatives with carbonyl group as the important structural feature.

5. Experimental

5.1. Chemistry

5.1.1. General

Melting points were determined on a Boetius-type Kofler block and are not corrected. The ^{1}H NMR spectra of 6% solutions of the compounds and ^{13}C NMR spectra of 20% solutions of the compounds in $CDCl_3$ (or in DMSO-d_6) containing TMS or 3-(trimethylsilyl)propanoic acid-d_5 as the internal standard were measured on a Bruker-250-DXP, 250 MHz spectrometer. Chemical shifts are given in the δ-scale (ppm) and coupling constants J in hertz.

The purity of compounds **1**–**11**, **13**–**35** was evaluated by HPLC on an Alliance Waters 2695 liquid chromatograph (Waters Associates, Milford, MA, USA) with UV detection (Waters 2487 dual detector) at 225 nm. Cromasil C18 100A (300 mm × 4.6 mm) was obtained from Chromservis (Czech Republic). Gradient chromatography was performed with water (Q plus, Millipore, Germany) and acetonitrile (Merck, Darmstadt) with 0.1% of phosphoric acid (Merck, Darmstadt) as a mobile phase. The eluent flow-rate was 1 ml/min. The purity of compounds **1**–**11** was higher than 98.0% and the purity of compounds **13**–**37** was higher than 95.0% with the exception of **27b**, **27c**, **28b**, **28c**, **31b**, **31c**, **33b** where 90% of purity was attained. The structures of esters **25b**–**35c** were confirmed by ^{1}H NMR spectra summarized in Table 4.

5.1.2. Synthesis of 2-[(4-ω-halogenalkoxy)phenyl]-N-methyl-N-phenethylacetamides *13*

To a mixture of 2-(4-hydroxyphenyl)-*N*-methyl-*N*-phenethylacetamide (**12**, 0.0037 mol), potassium carbonate (2.6 g), 18-crown-6 (0.05 g) in butan-2-one (25 ml), was added 1-chloro-2-tosylethane or appropriate 1,ω-dibromoalkane (0.0046 mol). The mixture was stirred under reflux and controlled by TLC, using chloroform–benzene–acetic acid (60:40:5) as the eluent. The solution was filtered and evaporated. The crude product was chromatographed on silica gel (dichloromethane–ethylacetate, 1:1).

Table 4
^{1}H NMR spectra of esters **25b–35c**

Compound	^{1}H NMR spectrum
25b	1.37 (d, $J = 7.2$, 3H); 2.16 (m, 2H); 2.74 (t, $J = 7.2$; 2H); 2.85 (s, 1.5H); 2.90 (s, 1.5H); 3.37 (s, 1H); 3.50 (t, $J = 7.5$, 1H); 3.59 (t, $J = 7.6$, 1H); 3.57 (s, 1H); 3.58 (s, 3H); 3.73 (q, $J = 7.1$, 1H); 4.12 (m, 4H); 6.84–6.94 (m, 4H); 7.01 (d, $J = 8.7$, 1H); 7.09 (d, $J = 8.6$, 1H); 7.17–7.32 (m, 7H)
25c	1.47 (d, $J = 7.2$, 3H); 1.96 (m, 4H); 2.73 (t, $J = 7.3$, 1H); 2.83 (t, $J = 7.4$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.65 (s, 3H); 3.67 (q, $J = 7.1$, 1H); 4.02 (m, 4H); 6.82–6.86 (m, 4H); 7.05–7.25 (m, 9H)
26b	1.46 (d, $J = 7.3$, 3H); 2.28 (m, 2H); 2.73 (t, $J = 7.3$, 1H); 2.85 (s, 1.5H); 2.86 (t, $J = 7.5$, 1H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.47 (t, $J = 7.4$, 1H); 3.59 (t, $J = 7.6$, 1H); 3.61 (s, 1H); 3.63 (q, $J = 7.2$, 1H); 3.65 (s, 3H); 4.19 (m, 4H); 6.81–6.91 (m, 3H); 7.03–7.31 (m, 9H)
26c	1.45 (d, $J = 7.0$, 3H); 2.02 (m, 4H); 2.71 (t, $J = 7.4$, 1H); 2.83 (t, $J = 7.2$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 3.63 (q, $J = 7.1$, 1H); 3.66 (s, 3H); 4.08 (m, 4H); 6.79–6.87 (m, 3H); 7.01–7.29 (m, 9H)
27b	2.24 (m, 2H); 2.62 (t, $J = 7.4$, 2H); 2.74 (t, $J = 7.4$, 1H); 2.84 (t, $J = 7.4$, 1H); 2.89 (s, 1.5H); 2.90 (t, $J = 7.5$, 2H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.6$, 1H); 3.59 (t, $J = 7.7$, 1H); 3.61 (s, 1H); 3.66 (s, 3H); 4.13 (m, 4H); 6.84 (m, 4H); 7.02–7.34 (m, 9H)
27c	1.96 (m, 4H); 2.60 (t, $J = 7.2$, 2H); 2.80 (t, $J = 7.1$, 1H); 2.87 (t, $J = 7.3$, 1H); 2.89 (s, 1.5H); 2.90 (t, $J = 7.1$, 2H); 2.98 (s, 1.5H); 3.39 (s, 1H); 3.53 (m, 2H); 3.62 (s, 1H); 3.66 (s, 3H); 3.99 (m, 4H); 6.81–6.86 (m, 4H); 7.02–7.30 (m, 9H)
28b	2.21 (m, 2H); 2.63 (t, $J = 7.7$, 2H); 2.74 (t, $J = 7.5$, 1H); 2.85 (t, $J = 7.4$, 1H); 2.86 (s, 1.5H); 2.89 (t, $J = 7.8$, 2H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.67 (s, 3H); 3.82 (s, 3H); 4.16 (m, 4H); 6.72 (m, 2H); 6.84 (m, 3H); 7.04–7.26 (m, 7H)
28c	1.98 (m, 4H); 2.64 (t, $J = 8.2$, 2H); 2.73 (t, $J = 7.3$, 1H); 2.84 (t, $J = 7.4$, 1H); 2.86 (s, 1.5H); 2.86 (t, $J = 8.1$, 2H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.2$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.67 (s, 3H); 3.84 (s, 3H); 4.05 (m, 4H); 6.73 (m, 2H); 6.81–6.87 (m, 3H); 7.10–7.30 (m, 7H)
29b	1.13 (d, $J = 6.7$, 3H); 2.23 (m, 2H); 2.59 (t, $J = 7.6$, 2H); 2.67 (t, $J = 7.4$, 1H); 2.76 (t, $J = 7.3$, 1H); 2.83 (s, 1.5H); 2.86 (q, $J = 6.9$, 1H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.5$, 1H); 3.58 (t, $J = 7.5$, 1H); 3.62 (s, 1H); 3.64 (s, 3H); 4.13 (m, 4H); 6.80–6.87 (m, 4H); 7.04–7.25 (m, 9H)
29c	1.13 (d, $J = 6.6$, 3H); 1.95 (m, 4H); 2.59 (d, $J = 6.9$, 1H); 2.65 (d, $J = 6.7$, 1H); 2.74 (t, $J = 7.0$, 1H); 2.80 (t, $J = 7.2$, 1H); 2.74 (s, 1.5H); 2.90 (q, $J = 6.9$, 1H); 2.95 (s, 1.5H); 3.35 (s, 1H); 3.49 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.4$, 1H); 3.59 (s, 1H); 3.62 (s, 3H); 4.01 (m, 4H); 6.78–6.83 (m, 4H); 7.04–7.27 (m, 9H)
30a	1.95 (m, 2H); 2.31 (t, $J = 7.4$, 2H); 2.54 (t, $J = 7.5$, 2H); 2.74 (t, $J = 7.3$, 1H); 2.84 (t, $J = 7.3$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.60 (t, $J = 7.5$, 1H); 3.60 (s, 1H); 3.66 (s, 3H); 4.30 (m, 4H); 6.86–7.05 (m, 4H); 7.09–7.29 (m, 9H)
30b	1.93 (m, 2H); 2.23 (m, 2H); 2.31 (t, $J = 7.4$, 2H); 2.58 (t, $J = 7.5$, 2H); 2.69 (t, $J = 7.4$, 1H); 2.76 (t, $J = 7.5$, 1H); 2.83 (s, 1.5H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.5$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.60 (s, 1H); 3.65 (s, 3H); 4.12 (m, 4H); 6.80–6.85 (m, 4H); 7.03–7.26 (m, 9H)
30c	1.86–2.04 (m, 6H); 2.31 (t, $J = 7.5$, 2H); 2.58 (t, $J = 7.5$, 2H); 2.74 (t, $J = 7.3$, 1H); 2.83 (t, $J = 7.1$, 1H); 2.86 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.51 (t, $J = 7.5$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.66 (s, 3H); 4.00 (m, 4H); 6.80–6.86 (m, 4H); 7.06–7.28 (m, 9H)
31a	1.17 (d, $J = 7.0$, 3H); 1.62 (m, 1H); 1.97 (m, 1H); 2.48 (m, 1H); 2.58 (t, $J = 5.0$, 2H); 2.74 (t, $J = 7.0$, 1H); 2.83 (t, $J = 7.1$, 1H); 2.86 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.5$, 1H); 3.61 (t, $J = 7.5$, 1H); 3.62 (s, 1H); 3.67 (s, 3H); 4.28 (m, 4H); 6.88–6.91 (m, 4H); 7.08–7.26 (m, 9H)
31b	1.16 (d, $J = 7.0$, 3H); 1.67 (m, 1H); 1.92 (m, 1H); 2.20 (m, 2H); 2.43 (m, 1H); 2.53 (t, $J = 7.9$, 2H); 2.73 (t, $J = 7.3$, 1H); 2.79 (t, $J = 7.4$, 1H); 2.80 (s, 1.5H); 2.94 (s, 1.5H); 3.36 (s, 1H); 3.47 (t, $J = 7.4$, 1H); 3.57 (t, $J = 7.5$, 1H); 3.58 (s, 1H); 3.64 (s, 3H); 4.10 (m, 4H); 6.77–6.87 (m, 4H); 7.04–7.26 (m, 9H)
31c	1.18 (d, $J = 7.0$, 3H); 1.70 (m, 1H); 1.96 (m, 5H); 2.55 (m, 1H); 2.58 (t, $J = 7.9$, 2H); 2.74 (t, $J = 7.3$, 1H); 2.84 (t, $J = 7.5$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.60 (t, $J = 7.5$, 1H); 3.61 (s, 1H); 3.67 (s, 3H); 4.00 (m, 4H); 6.80–6.86 (m, 4H); 7.06–7.26 (m,)
32a	2.75 (t, $J = 6.8$, 2H); 2.82 (m, 2H); 2.86 (s, 1.5H); 2.98 (s, 1.5H); 3.27 (t, $J = 6.7$, 2H); 3.39 (s, 1H); 3.51 (t, $J = 7.6$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 3.70 (s, 3H); 4.35 (m, 4H); 6.85 (m, 2H); 6.97 (m, 2H); 7.07–7.34 (m, 7H); 7.95 (m, 2H)
33a	2.75 (t, $J = 6.8$, 2H); 2.82 (m, 2H); 2.86 (s, 1.5H); 2.98 (s, 1.5H); 3.27 (t, $J = 6.7$, 2H); 3.39 (s, 1H); 3.51 (t, $J = 7.6$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 3.70 (s, 3H); 4.35 (m, 4H); 6.85 (m, 2H); 6.97 (m, 2H); 7.07–7.34 (m, 7H); 7.95 (m, 2H)
33b	2.26 (m, 2H); 2.73 (m, $J = 7.2$, 1H); 2.83 (m, $J = 7.2$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.5$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.79 (s, 3H); 4.16 (m, 4H); 6.30 (d, $J = 16.2$, 1H); 6.83–6.93 (m, 4H); 7.08–7.28 (m, 7H); 7.45 (d, $J = 8.6$, 2H); 7.64 (d, $J = 16.1$, 1H)
33c	1.97 (m, 4H); 2.74 (t, $J = 7.2$, 1H); 2.83 (t, $J = 7.0$, 1H); 2.86 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.51 (t, $J = 7.5$, 1H); 3.60 (t, $J = 7.5$, 1H); 3.61 (s, 1H); 3.79 (s, 3H); 4.03 (m, 4H); 6.30 (d, $J = 16.0$, 1H); 6.82–6.92 (m, 4H); 7.07–7.29 (m, 7H); 7.46 (m, 2H); 7.65 (d, $J = 16.0$, 1H)
34a	2.75 (t, $J = 7.3$, 1H); 2.82 (t, $J = 7.5$, 1H); 2.83 (s, 1.5H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.51 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 3.80 (s, 3H); 3.88 (s, 3H); 4.37 (m, 4H); 6.35 (d, $J = 16.0$, 1H); 6.87–6.90 (m, 3H); 7.04–7.30 (m, 9H); 7.63 (d, $J = 16.0$, 1H)
34b	2.30 (m, 2H); 2.67 (t, $J = 7.3$, 1H); 2.79 (t, $J = 7.4$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.37 (s, 1H); 3.53 (t, $J = 7.4$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.80 (s, 3H); 3.88 (s, 3H); 4.16 (m, 4H); 6.27 (d, $J = 15.9$, 1H); 6.80–6.91 (m, 3H); 7.02–7.34 (m, 7H); 7.62 (d, $J = 16.0$, 1H)
34c	2.01 (m, 2H); 2.75 (t, $J = 7.4$, 1H); 2.83 (t, $J = 7.3$, 1H); 2.86 (s, 1.5H); 2.98 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.61 (t, $J = 7.5$, 1H); 3.62 (s, 1H); 3.80 (s, 3H); 3.84 (s, 3H); 4.12 (m, 4H); 6.31 (d, $J = 15.9$, 1H); 6.83–6.86 (m, 3H); 7.04–7.27 (m, 9H); 7.64 (d, $J = 15.9$, 1H)
35a	1.57 (d, $J = 7.2$, 3H); 2.30 (m, 2H); 2.73 (t, $J = 7.3$, 1H); 2.80 (t, $J = 7.3$, 1H); 2.84 (s, 1.5H); 2.96 (s, .5H); 3.38 (s, 1H); 3.49 (t, $J = 7.3$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.61 (s, 1H); 3.66 (s, 3H); 3.86 (q, $J = 7.2$, 1H); 4.17 (m, 2H); 4.25 (m, 2H); 6.86 (m, 2H); 7.02–7.38 (m, 10H); 7.61–7.65 (m, 3H)

(*continued on next page*)

Table 4 (*continued*)

Compound	^{1}H NMR spectrum
35b	1.57 (d, $J = 7.1$, 3H); 2.01 (m, 4H); 2.74 (t, $J = 7.1$, 1H); 2.83 (t, $J = 7.2$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.1$, 1H); 3.61 (s, 1H); 3.66 (s, 3H); 3.81 (q, $J = 7.2$, 1H); 4.04 (m, 2H); 4.09 (m, 2H); 6.86 (m, 2H); 7.03–7.34 (m, 10H); 7.61–7.66 (m, 3H (H18, 19, 22)).
35c	1.57 (d, $J = 7.1$, 3H); 2.01 (m, 4H); 2.74 (t, $J = 7.1$, 1H); 2.83 (t, $J = 7.2$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.1$, 1H); 3.61 (s, 1H); 3.66 (s, 3H); 3.81 (q, $J = 7.2$, 1H); 4.04 (m, 2H); 4.09 (m, 2H); 6.86 (m, 2H); 7.03–7.34 (m, 10H); 7.61–7.66 (m, 3H)

*5.1.2.1. 2-[4-(2-Chloroethoxy)phenyl]-N-methyl-N-phenethylacetamide **13a***. Yellowish oil (1.1 g, 89%). Anal Calcd. for $C_{19}H_{22}ClNO_2$ (331.8): C, 68.77; H, 6.68; N, 4.22; found: C, 68.59; H, 6.75; N, 4.19%. ^{1}H NMR ($CDCl_3$) δ: 2.75 (t, $J = 7.4$, 1H); 2.83 (t, $J = 7.2$, 1H); 2.86 (s, 1.5H); 2.97 (s, 1.5H); 3.37 (s, 1H); 3.48 (t, $J = 7.4$, 1H); 3.59 (t, $J = 7.3$, 1H); 3.62 (s, 1H); 3.80 (m, 2H); 4.22 (m, 2H); 6.86 (m, 2H); 7.19–7.29 (m, 7H).

*5.1.2.2. 2-[4-(3-Bromopropoxy)phenyl]-N-methyl-N-phenethylacetamide **13b***. Yellowish oil (1.1 g, 80%). Anal Calcd. for $C_{20}H_{24}BrNO_2$ (390.3): C, 61.54; H, 6.20; N, 3.59; found: C, 61.45; H, 6.21; N, 3.57%. ^{1}H NMR ($CDCl_3$) δ: 2.10 (m, 2H); 2.81 (t, $J = 7.2$, 1H); 2.85 (t, $J = 7.5$, 1H); 2.97 (s, 1.5H); 3.39 (s, 1.5H); 3.39 (s, 1H); 3.51 (m, $J = 7.5$, 1H); 3.58 (t, $J = 7.3$, 1H); 3.59 (m, 2H); 3.60 (s, 1H); 4.08 (m, 2H); 6.85 (m, 2H); 7.06–7.23 (m, 7H).

*5.1.2.3. 2-[4-(4-Bromobutoxy)phenyl]-N-methyl-N-phenethylacetamide **13c***. Yellowish oil (1.5 g, 85%). Anal Calcd. for $C_{21}H_{26}BrNO_2$ (404.3): C, 62.38; H, 6.48; N, 3.46; found: C, 62.28; H, 6.50; N, 3.44%. ^{1}H NMR ($CDCl_3$) δ: 1.90 (m, 2H); 2.00 (m, 2H); 2.74 (t, $J = 7.4$, 1H); 2.83 (t, $J = 7.5$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.38 (s, 1H); 3.48 (m, 2H); 3.49 (t, $J = 7.3$, 1H); 3.59 (t, $J = 7.6$, 1H); 3.60 (s, 1H); 3.98 (m, 2H); 6.82 (m, 2H); 7.06–7.23 (m, 7H).

*5.1.3. Synthesis of methyl (3-X-4-hydroxyphenyl)alkanoates **14–16, 18–21, 24***

To a mixture of (3-X-4-methoxyphenyl)alkanoic acid (0.052 mol) in dichloromethane (190 ml) cooled to −65 °C, 1.75 N solution of boron tribromide in dichloromethane (44.2 ml, 0.078 mol) was added dropwise during 20 min. The mixture was then spontaneously heated to the ambient temperature, stirred for 2.5 h and poured in ice (200 g). Water layer was washed by ethyl acetate (100 ml) and combined organic layers were washed with water (2 × 200 ml), dried with magnesium sulfate, filtered and evaporated. Pure acid was obtained by crystallization of crude acid and its mixture (0.043 mol) and 4-toluensulfonic acid (0.8 g, 0.045 mol) in methanol (100 ml) was refluxed for 14 h and evaporated. The oily residue was dissolved in ethyl acetate, washed with 10% solution of $NaHCO_3$, and the dried organic layer was filtered and evaporated. The crude product was purified by chromatography on silica gel with appropriate eluent to give the desired pure ester.

*5.1.3.1. Methyl 2-(4-hydroxyphenyl)propanoate (**14**)*. The crude acid was crystallized from water to give pure acid in 90.0% yield, m.p. 126–129 °C (lit. [26] m.p. 128–129 °C). The crude **14** was purified by chromatography (eluent: petroleum ether–ethyl acetate) to give pure ester **14** in 55% yield; yellowish oil, b.p. 168–174 °C/0.93 kPa (lit. [29] b.p. 170–175 °C/0.93 kPa). ^{1}H NMR ($CDCl_3$) δ: 1.47 (d, $J = 7.2$, 3H); 3.66 (s, 3H); 3.68 (q, $J = 7.1$, 1H); 6.76 (d, $J = 8.6$, 2H); 7.14 (d, $J = 8.3$; 2H).

*5.1.3.2. Methyl 2-(3-chloro-4-hydroxyphenyl)propanoate (**15**)*. The crude acid, isolated as oil, was used without purification in the next step. ^{1}H NMR ($CDCl_3$) δ: 1.47 (d, $J = 7.2$, 3H); 3.65 (q, $J = 7.2$, 1H); 6.96 (d, $J = 8.6$, 1H); 7.11 (d, $J = 8.8$, 1H); 7.28 (s, 1H). The crude **15**, purified by chromatography (eluent: petroleum ether–ethyl acetate), gave 82% of pure **15**; yellowish oil, b.p. 89 °C/0.16 kPa (lit. [26] b.p. 88–90 °C/0.16 kPa). ^{1}H NMR ($CDCl_3$) δ: 1.46 (d, $J = 7.2$, 3H); 3.65 (q, $J = 7.1$, 1H); 3.67 (s, 3H); 5.63 (br s, 1H); 6.95 (d, $J = 8.4$, 1H); 7.12 (d, $J = 8.3$, 1H); 7.26 (s, 1H).

*5.1.3.3. Methyl 3-(4-hydroxyphenyl)propanoate (**16**)*. The crude acid was crystallized from water to give pure acid in 59% yield, m.p. 125–128 °C (lit. [26] m.p. 124–126 °C). The crude **16** purified by chromatography (eluent: petroleum ether–ethyl acetate used) gave pure **16** in 86% yield; colourless oil, b.p. 86–89 °C/0.085 kPa (lit. [26] b.p. 90 °C/0., 085 kPa). ^{1}H NMR ($CDCl_3$) δ: 2.60 (t, $J = 7.5$, 2H); 2.88 (t, $J = 7.7$, 2H); 3.67 (s, 3H); 5.48 (br s, 1H); 6.76 (d, $J = 6.6$, 2H); 7.03 (d, $J = 6.4$, 2H).

*5.1.3.4. Methyl 3-(4-hydroxyphenyl)-2-methylpropanoate (**18**)*. The crude acid was crystallized from toluene–cyclohexane to give pure acid in 82% yield, m.p. 97–99 °C (lit. [30] m.p. 99 °C). The crude **18** purified by chromatography (eluent: dichloromethane–ethyl acetate used) gave pure **18** in 87% yield; yellowish oil, b.p. 83–87 °C/0.085 kPa. Anal Calcd. for $C_{11}H_{14}O_3$ (194.2): C, 68.02; H, 7.27; found: C, 68.21; H, 7.25.

^{1}H NMR ($CDCl_3$) δ: 1.14 (d, $J = 6.8$, H); 2.61–2.91 (m, 2H); 2.71 (m, 1H); 3.63 (s, 3H); 6.74 (d, $J = 8.5$, 2H); 6.98 (d, $J = 8.5$, 2H).

*5.1.3.5. Methyl 4-(4-hydroxyphenyl)butanoate (**19**)*. The crude acid was crystallized from water to give pure acid in 87% yield, m.p. 104–105 °C (lit. [31] m.p. 110–111 °C). Crude **19** was purified by chromatography (eluent: dichloromethane–ethyl acetate) which gave pure **19** in 76% yield; yellowish oil, b.p. 161–165 °C/0.40 kPa (lit. [32] b.p. 163–164 °C/0.40 kPa).

^{1}H NMR ($CDCl_3$) δ: 1.89 (m, 2H); 2.31 (t, $J = 7.5$, 2H); 2.53 (t, $J = 7.5$, 2H); 3.65 (s, 3H); 6.24 (br s, 1H); 6.77 (d, $J = 8.4$, 2H); 6.97 (d, $J = 8.4$, 2H).

*5.1.3.6. Methyl 4-(4-hydroxyphenyl)-2-methylbutanoate (**20**).* The crude acid was crystallized from toluene–*n*-hexane to give pure acid in 62% yield, m.p. 59–62 °C. Anal Calcd. for $C_{11}H_{14}O_3$ (194.2): C, 68.02; H, 7.27; found: C, 68.25; H, 7.16. ^{1}H NMR ($CDCl_3$) δ: 1.20 (d, $J = 7.1$, 3H); 1.68 (m, 1H); 1.97 (m, 1H); 2.48 (m, 1H); 2.55 (m, 1H); 6.75 (d, $J = 9.3$, 2H); 7.00 (d, $J = 9.4$, 2H). Crude **20** purified by chromatography (eluent: dichloromethane–ethyl acetate) gave pure **20** in 91% yield; colourless oil, b.p. 156–160 °C/0.40 kPa. Anal Calcd. for $C_{12}H_{16}O_3$ (208.2): C, 69.21; H, 7.74; found: C, 69.28; H, 7.69. ^{1}H NMR ($CDCl_3$): 1.17 (d, $J = 6.9$, 3H); 1.68 (m, 1H); 1.96 (m, 1H); 2.50 (m, 2H); 3.67 (s, 3H); 6.79 (d, $J = 8.5$, 2H); 6.99 (d, $J = 8.6$, 2H).

*5.1.3.7. Methyl 3-(4-hydroxyphenyl)-3-oxobutanoate (**21**).* The crude acid was crystallized from water to give pure acid in 66% yield; m.p. 156–159 °C (lit. [33] m.p. 160–161 °C). Crude **21** purified by crystallization from toluene gave pure **21** in 54% yield; dark yellow crystals, m.p. 117–117.5 °C (lit. [27] m.p. 114–117 °C). ^{1}H NMR ($CDCl_3$) δ: 2.77 (t, $J = 6.6$, 2H); 3.26 (t, $J = 6.6$, 2H); 3.72 (s, 3H); 6.84 (d, $J = 6.8$, 2H); 7.83 (d, $J = 6.8$, 2H).

*5.1.3.8. Methyl 2-(7-hydroxy-2-naphthyl)propanoate (**24**).* The crude acid was crystallized from toluene to give the pure acid in 68% yield, m.p. 179–181 °C (lit. [34] m.p. 179–181 °C). Crude **24** purified by chromatography (eluent: petroleum ether–ethyl acetate) gave pure **24** in 86% yield. Anal Calcd. for $C_{14}H_{14}O_3$ (230.3): C, 73.03; H, 6.13; found: C, 73.08; H, 6.11. ^{1}H NMR ($CDCl_3$) δ: 1.58 (d, $J = 7.2$, 3H); 3.69 (s, 3H); 3.79 (q, $J = 7.2$, 1H); 5.68 (br s, 1H); 7.1 (m, 2H); 7.39 (m, 1H); 7.60–7.69 (m, 3H).

*5.1.4. Methyl 4-hydroxycinnamate (**17**)*

Crude 4-hydroxycinnamic acid, prepared [35] from 4-hydroxybenzaldehyde and malonic acid, was purified by crystallization from aqueous ethanol in yield of 85% giving white crystals with m.p. 208–209 °C (lit. [35] m.p. 207 °C). Esterification in methanol in the presence of 4-toluensulfonic acid afforded crude ester **22**, purified by crystallization from toluene to give pure **22** in 95% yield; pale yellow crystals, m.p. 134–136 °C (lit. [36] m.p. 138 °C). ^{1}H NMR ($CDCl_3$) δ: 3.81 (s, 3H); 5.75 (br s, 1H); 6.25 (d, $J = 16.2$, 1H); 6.87 (m, 2H); 7.43 (m, 2H); 7.64 (d, $J = 16.5$, 1H).

*5.1.5. Methyl 4-hydroxy-3-methoxycinnamate (**22**)*

Crude 4-hydroxy-3-methoxycinnamic acid, prepared [37] from vanilline and malonic acid afforded by crystallization from ethanol, the pure acid in 86% yield, m.p. 169–171 °C (lit. [37] m.p. 171 °C). Esterification in methanol in the presence of 4-toluensulfonic acid afforded crude ester **23**, purified by crystallization from petroleum ether–diethyl ether to give pure **23** in 90% yield; white precipitate, with m.p. 63–65 °C (lit. [38] m.p. 65.5–66.5 °C). ^{1}H NMR ($CDCl_3$) δ: 3.79 (s, 3H); 3.91 (s, 3H); 6.29 (d, $J = 15.9$, 1H); 6.90 (d, $J = 8.1$, 1H); 7.03 (m, 2H); 7.62 (d, $J = 15.9$, 1H).

*5.1.6. Methyl 3-(4-hydroxy-3-methoxyphenyl)propanoate (**23**)*

The pure 3-(4-hydroxy-3-methoxyphenyl)propanoic acid (m.p. 91 °C; lit. [37] m.p. 90.5–91.5 °C) prepared in 91% yield by hydrogenation [35] of 4-hydroxy-3-methoxycinnamic acid with 5% palladium on charcoal, was refluxed in methanol with 4-toluensulfonic acid for 14 h. Purification by chromatography on silica gel (eluent: petroleum ether–ethyl acetate) gave 89% of pure **17**; yellowish oil with b.p. 145–147 °C/0.40 kPa (lit. [35] b.p. 148–150 °C/0.40–0.53 kPa). ^{1}H NMR ($CDCl_3$) δ: 2.60 (t, $J = 7.3$, 2H); 2.88 (t, $J = 7.2$, 2H); 3.67 (s, 3H); 3.86 (s, 3H); 5.48 (br s, 1H); 6.70 (m, 2H); 6.82 (d, $J = 6.6$, 1H).

*5.1.7. Synthesis of arylalkanoic acids **1b–11b***

To a mixture of **13** (0.010 mol), potassium carbonate (3.5 g), and potassium iodide (0.12 g) in 4-methylpentan-2-one (40 ml), **14–24** (0.011 mol) was added. The mixture was refluxed for 6 h and then filtered and evaporated. The crude esters **25–35** were purified either by crystallization or by column chromatography on silica gel. Their purity was evaluated by HPLC, and their structure confirmed by ^{1}H NMR spectra.

To a mixture of esters **25–35** (0.005 mol) in 20 ml of tetrahydrofuran/water 4:1 1.80 g of lithium hydroxide was added. The mixture was stirred at ambient temperature overnight. After evaporation of tetrahydrofuran, the crude product was dissolved in water (50 ml) and acidified with acetic acid and filtered. The crude acids were purified by crystallization from appropriate solvents.

*5.1.7.1. 2-[4-(3-{4-[(Phenethylcarbamoyl)methyl]phenoxy}propoxy)phenyl] propanoic acid, cyclohexylammonium salt **1b**.* Hydrolysis of **25b** [white powder (3.1 g, 64%); m.p. 73–76 °C (dichloromethane–ethyl acetate)] afforded crude acid as glassy oil, which was purified as cyclohexylammonium salt (4.9 g, 92%); m.p. 128–131 °C (acetone–diethyl ether). Anal Calcd. for $C_{35}H_{46}N_2O_5 \cdot 2H_2O$ (610.8): C, 68.83; H, 8.25; N, 4.59; found: C, 68.63; H, 8.46; N, 4.81%. ^{1}H NMR ($CDCl_3$, free acid) δ: 1.47 (d, $J = 7.2$, 3H); 2.21 (m, 2H); 2.76 (t, $J = 6.9$, 1H); 2.83 (t, $J = 7.1$, 1H); 2.83 (s, 1.5H); 2.97 (s, 1.5H); 3.50 (s, 1H); 3.50 (t, $J = 7.2$, 1H); 3.61 (t, $J = 7.1$, 1H); 3.63 (s, 1H); 3.66 (q, $J = 7.0$, 1H); 4.13 (m, 4H); 6.74–6.87 (m, 4H); 6.97–7.08 (m, 2H); 7.10–7.16 (m, 2H); 7.19–7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.1, 22.8, 28.0, 29.2, 33.1, 34.8, 36.4, 38.3, 42.8, 50.3, 50.8, 65.1, 114.7, 114.9, 125.9, 127.0, 127.5, 127.6, 128.7, 130.1, 139.4, 156.2, 156.5, 160.7, 177.5.

*5.1.7.2. 2-[4-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy}butoxy)phenyl] propanoic acid **1c**.* Hydrolysis of **25c** [yellowish solid (4.2 g, 85%); m.p. 59–61 °C (ethyl acetate–petrol

ether)] afforded pure acid **1c** as white precipitate (3.6 g, 87%), m.p. 102–103 °C (ethyl acetate–diethyl ether). Anal Calcd. for $C_{30}H_{35}NO_5$ (489.6): C, 73.59; H, 7.21; N, 2.86; found: C, 73.36; H, 7.08; N, 2.96%. ^{1}H NMR ($CDCl_3$) δ: 1.47 (d, $J = 7.2$, 3H); 1.95 (m, 4H); 2.73 (t, $J = 7.4$, 1H); 2.83 (t, $J = 7.5$, 1H); 2.84 (s, 1.5H); 2.97 (s, 1.5H); 3.40 (s, 1H); 3.47 (t, $J = 7.6$, 1H); 3.57 (t, $J = 7.5$, 1H); 3.61 (s, 1H); 3.64 (q, $J = 7.3$, 2H); 4.01 (m, 4H); 6.77–6.85 (m, 4H); 6.99–7.18 (m, 4H); 7.17–7.26 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 16.2, 22.9, 26.1, 28.0, 29.4, 33.2, 34.7, 36.5, 38.5, 42.7, 50.4, 50.9, 68.9, 114.1, 114.5, 125.9, 126.9, 127.3, 127.4, 127.7, 128.7, 130.2, 139.6, 156.3, 156.4, 160.7, 177.5.

*5.1.7.3. 2-[3-Chloro-4-(3-{4-[(phenethylcarbamoyl)methyl] phenoxy}propoxy)phenyl] propanoic acid, cyclohexylammonium salt **2b***. Hydrolysis of **26b** [yellowish solid (3.6 g, 69%); m.p. 60–63 °C (ethyl acetate–petrol ether)] afforded crude acid as glassy oil, which was isolated and purified as cyclohexylammonium salt (1.7 g, 40%); m.p. 108–110 °C (acetone). Anal Calcd. for $C_{35}H_{45}ClN_2O_5$ (609.2): C, 69.00; H, 7.45; N, 4.60; found: C, 69.13; H, 7.47; N, 4.65%. ^{1}H NMR ($CDCl_3$ free acid) δ: 1.45 (d, $J = 7.2$, 3H); 2.23 (m, 2H); 2.74 (t, $J = 7.2$, 1H); 2.83 (t, $J = 7.4$, 1H); 2.83 (s, 1.5H); 2.98 (s, 1.5H); 3.38 (s, 1H); 3.47 (t, $J = 7.6$, 1H); 3.59 (t, $J = 7.4$, 1H); 3.60 (s, 1H); 3.61 (q, $J = 7.0$, 1H); 4.22 (m, 4H); 6.73–6.77 (m, 2H); 6.83–6.87 (m, 1H); 6.95 (d, $J = 8.7$, 1H); 7.01 (d, $J = 8.8$, 1H); 7.06–7.11 (m, 2H); 7.14–7.32 (m, 5H). ^{13}C NMR ($CDCl_3$ free acid) δ: 16.2, 22.8, 27.9, 29.0, 33.1, 35.0, 36.5, 38.2, 42.2, 50.1, 50.6, 64.8, 65.3, 114.8, 116.1, 123.0, 125.9, 127.1, 127.7, 128.4, 128.7, 130.3, 139.6, 150.2, 156.7, 160.7, 177.5.

*5.1.7.4. 2-[3-Chloro-4-(4-{4-[(phenethylcarbamoyl)methyl] phenoxy}butoxy)phenyl] propanoic acid **2c***. Hydrolysis of **26c** [yellowish solid (4.0 g, 75%); m.p. 56–58 °C (ethyl acetate–petrol ether)] afforded pure acid **2c** as white precipitate (2.3 g, 59%); m.p. 99–100 °C (ethyl acetate–petrol ether). Anal Calcd. for $C_{30}H_{34}ClNO_5$ (524.1): C, 68.76; H, 6.54; N, 2.67; found: C, 68.61; H, 6.57; N, 2.70%. ^{1}H NMR ($CDCl_3$) δ: 1.46 (d, $J = 6.9$, 3H); 1.99 (m, 4H); 2.74 (t, $J = 7.4$, 1H); 2.84 (t, $J = 7.3$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.40 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.56 (t, $J = 7.5$, 1H); 3.57 (m, 1H); 3.61 (s, 1H); 4.09 (m, 4H); 6.67 (m, 2H); 6.77 (m, 1H); 6.92–7.28 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 16.2, 25.9, 33.2, 34.8, 36.4, 38.2, 42.4, 50.1, 50.7, 68.5, 68.8, 114.9, 116.1, 123.2, 126.0, 127.5, 127.9, 128.5, 128.8, 130.2, 130.4, 139.5, 150.2, 156.4, 160.9, 177.5.

*5.1.7.5. 3-[4-(3-{4-[(Phenethylcarbamoyl)methyl]phenoxy} propoxy)phenyl] propanoic acid **3b***. Hydrolysis of **27b** [yellowish solid (3.0 g, 63%); m.p. 79–81 °C (acetone)] afforded pure acid **3b** as white precipitate (2.1 g, 70%); m.p. 100–102 °C (ethyl acetate). Anal Calcd. for $C_{29}H_{33}NO_5 \cdot H_2O$ (507.6): C, 70.98; H, 7.35; N, 2.76; found: C, 70.72; H, 7.24; N, 2.84%. ^{1}H NMR ($CDCl_3$) δ: 2.20 (m, 2H); 2.62 (t, $J = 7.5$, 2H); 2.76 (t, $J = 7.5$, 1H); 2.84 (t, $J = 7.4$, 1H); 2.88 (s, 1.5H); 2.89 (t, $J = 7.4$, 2H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.57 (t, $J = 7.5$, 1H); 3.61 (t, $J = 7.5$, 1H); 3.62 (s, 1H); 4.13 (m, 4H); 6.79–6.84 (m, 4H); 6.97–7.34 (m, 9H). ^{13}C NMR ($CDCl_3$) δ: 29.1, 33.1, 33.6, 34.8, 36.5, 38.3, 50.8, 65.3, 114.1, 115.1, 126.01, 127.4, 127.9, 128.6, 128.8, 130.4, 131.3, 139.6, 154.7, 156.4, 160.9, 177.5.

*5.1.7.6. 3-[4-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy} butoxy)phenyl] propanoic acid **3c***. Hydrolysis of **27c** [yellowish solid (2.8 g, 56%); m.p. 68–71 °C (ethyl acetate–petrol ether)] afforded pure acid **3c** (1.8 g, 67%); m.p. 96–98 °C (ethyl acetate). Anal Calcd. for $C_{30}H_{35}NO_5$ (489.6): C, 73.59; H, 7.21; N, 2.86; found: C, 73.79; H, 7.24; N, 2.84%. ^{1}H NMR (DMSO-d_6) δ: 1.85 (m, 4H); 2.50 (t, $J = 7.2$, 2H); 2.84 (t, $J = 7.1$, 2H); 2.85 (t, $J = 7.4$, 2H); 2.86 (s, 1.5H); 2.91 (s, 1.5H); 3.46 (s, 1H); 3.51 (t, $J = 7.3$, 1H); 3.58 (t, $J = 7.2$, 1H); 3.59 (s, 1H); 4.00 (m, 4H); 6.82–6.86 (m, 4H); 6.89–7.17 (m, 4H); 7.19–7.37 (m, 5H). ^{13}C NMR ($CDCl_3$): 26.0, 33.1, 33.5, 34.8, 36.5, 38.3, 50.8, 68.9, 114.1, 114.8, 125.9, 127.5, 127.7, 128.4, 128.8, 130.3, 131.1, 139.6, 154.7, 156.6, 160.8, 177.4.

*5.1.7.7. 3-[3-Methoxy-4-(3-{4-[(phenethylcarbamoyl)methyl] phenoxy}propoxy)phenyl] propanoic acid **4b***. Hydrolysis of **28b** [yellowish solid (3.9 g, 76%); m.p. 48–50 °C (ethyl acetate–petrol ether)] afforded pure acid **4b** (3.6 g, 94%); m.p. 102–103 °C (ethyl acetate). Anal Calcd. for $C_{30}H_{37}NO_6$ (505.6): C, 71.27; H, 6.98; N, 2.77; found: C, 70.99; H, 6.95; N, 2.86%. ^{1}H NMR ($CDCl_3$) δ: 2.24 (m, 2H); 2.66 (t, $J = 7.7$, 2H); 2.73 (t, $J = 7.1$, 1H); 2.83 (t, $J = 7.2$, 1H); 2.84 (s, 1.5H); 2.89 (t, $J = 7.6$, 2H); 2.97 (s, 1.5H); 3.40 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.61 (t, $J = 7.3$, 1H); 3.62 (s, 1H); 3.82 (s, 3H); 4.17 (m, 4H); 6.74 (m, 2H); 6.79–6.84 (m, 3H); 7.06–7.15 (m, 3H); 7.16–7.29 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 29.1, 33.4, 33.9, 34.8, 36.5, 38.3, 50.8, 56.1, 65.3, 65.5, 112.4, 114.7, 115.1, 120.4, 126.2, 127.5, 127.9, 128.7, 130.4, 132.1, 139.4, 142.7, 149.7, 156.3, 160.8, 177.5.

*5.1.7.8. 3-[3-Methoxy-4-(4-{4-[(phenethylcarbamoyl)methyl] phenoxy}butoxy)phenyl] propanoic acid **4c***. Hydrolysis of **28c** [yellowish solid (3.2 g, 60%); m.p. 44–47 °C (ethyl acetate–petrol ether)] afforded pure **4c** (2.4 g, 76%); m.p. 92–94 °C (ethyl acetate). Anal Calcd. for $C_{31}H_{37}NO_6$ (503.6): C, 71.65; H, 7.18; N, 2.80; found: C, 71.98; H, 7.08; N, 2.76%. ^{1}H NMR ($CDCl_3$) δ: 1.98 (m, 4H); 2.64 (t, $J = 7.3$ H, 2H); 2.74 (t, $J = 7.4$, 1H); 2.84 (t, $J = 7.3$, 1H); 2.87 (s, 1.5H); 2.89 (t, $J = 7.3$, 2H); 2.97 (s, 1.5H); 3.41 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 3.82 (s, 3H); 4.04 (m, 4H); 6.73–6.83 (m, 5H); 7.08–7.28 (m, 7H). ^{13}C NMR ($CDCl_3$) δ: 26.0, 33.4, 33.9, 34.7, 36.3, 38.4, 50.8, 56.1, 68.9, 69.3, 112.3, 114.7, 115.4, 120.7, 126.1, 127.4, 127.8, 128.7, 130.4, 132.1, 139.6, 143.7, 149.9, 156.5, 160.7, 177.5.

*5.1.7.9. 2-Methyl-3-[(4-(3-{4-[(phenethylcarbamoyl)methyl] phenoxy}propoxy)phenyl] propanoic acid, cyclohexylammonium salt **5b***. Hydrolysis of **29b** [yellowish solid (4.8 g, 96%); m.p. 73–76 °C (ethyl acetate–dichloromethane)]

afforded crude acid as glassy oil, which was isolated and purified as cyclohexylammonium salt (1.2 g, 22%); m.p. 128–131 °C (ethyl acetate). Anal Calcd. for $C_{36}H_{48}N_2O_5$ (588.8): C, 73.44; H, 6.22; N, 4.76; found: C, 73.52; H, 6.24; N, 4.86%. ^{1}H NMR ($CDCl_3$ free acid) δ: 1.03 (d, $J = 6.5$, 3H); 1.87 (m, 2H); 2.52 (m, 1H); 2.75 (m, $J = 7.5$, 2H); 2.83 (t, $J = 7.3$, 1H); 2.84 (s, 1.5H); 2.87 (t, $J = 7.2$, 1H); 2.91 (s, 1.5H); 3.37 (s, 1H); 3.50 (t, $J = 7.2$, 1H); 3.56 (t, $J = 7.3$, 1H); 3.58 (s, 1H); 4.01 (m, 4H); 6.83–6.89 (m, 4H); 7.08–7.12 (m, 4H); 7.14–7.25 (m, 5H). ^{13}C NMR ($CDCl_3$ free acid): 16.2, 22.8, 27.9, 29.0, 33.2, 34.8, 36.4, 38.2, 39.7, 40.4, 50.2, 50.6, 65.1, 114.3, 114.7, 126.1, 127.1, 127.8, 128.6, 128.7, 129.6, 130.1, 139.5, 154.6, 156.3, 160.7, 178.5.

5.1.7.10. 2-Methyl-3-[4-(4-{4-[(phenethylcarbamoyl)methyl] phenoxy}butoxy)phenyl] propanoic acid ***5c***. Hydrolysis of **29c** [yellowish solid (3.0 g, 58%); m.p. 80–83 °C (ethyl–acetate–dichloromethane)] afforded pure acid **5c** (2.4 g, 83%); m.p. 115–116 °C (ethyl acetate–dichloromethane). Anal Calcd. for $C_{31}H_{37}NO_5$ (503.6): C, 73.93; H, 7.41; N, 2.78; found: C, 74.23; H, 7.41; N, 2.78%. ^{1}H NMR ($CDCl_3$) δ: 1.17 (d, $J = 6.9$, 3H); 1.94 (m, 4H); 2.60 (m, 2H); 2.71 (t, $J = 7.0$, 1H); 2.82 (t, $J = 7.1$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 2.98 (m, 1H); 3.40 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.60 (t, $J = 7.2$, 1H); 3.62 (s, 1H); 4.00 (m, 4H); 6.77–6.84 (m, 4H); 7.06–7.17 (m, 4H); 7.19–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.0, 16.2, 26.1, 33.3, 34.8, 36.3, 38.5, 39.8, 40.5, 50.2, 50.8, 68.7, 114.4, 114.9, 126.0, 127.5, 127.9, 128.7, 128.9, 129.6, 130.3, 139.8, 154.8, 156.4, 160.7, 178.7.

5.1.7.11. 4-[4-(2-{4-[(Phenethylcarbamoyl)methyl]phenoxy} ethoxy)phenyl] butanoic acid ***6a***. Hydrolysis of **30a** [yellowish solid (1.8 g, 36%); m.p. 85–87 °C (ethyl acetate–petrol ether)] afforded pure acid **6a** (1.6 g, 94%); m.p. 147–148 °C (ethyl acetate–diethyl ether). Anal Calcd. for $C_{29}H_{33}NO_5$ (475.6): C, 73.24; H, 6.99; N, 2.95; found: C, 72.97; H, 6.95; N, 2.81%. ^{1}H NMR ($CDCl_3$) δ: 1.76 (m, 2H); 2.21 (t, $J = 7.3$, 2H); 2.52 (t, $J = 7.4$; 2H); 2.76 (t, $J = 7.3$, 2H); 2.86 (s, 1.5H); 2.91 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.62 (t, $J = 7.3$, 1H); 3.60 (s, 1H); 4.27 (m, 4H); 6.88–6.94 (m, 4H); 6.99–7.17 (m, 4H); 7.21–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 25.1, 33.3, 34.9, 35.5, 35.8, 38.2, 50.6, 69.4, 114.4, 114.9, 126.1, 127.4, 127.9, 128.7, 128.9, 129.6, 130.3, 139.6, 154.7, 156.5, 160.9, 177.4.

5.1.7.12. 4-[4-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy} butoxy)phenyl] butanoic acid ***6b***. Hydrolysis of **30b** [yellowish solid (3.5 g, 70%); m.p. 65–67 °C (ethyl acetate)] afforded pure acid **6b** (3.0 g, 89%); m.p. 76–77 °C (toluene–*n*-hexane). Anal Calcd. for $C_{30}H_{35}NO_5$ (489.6): C, 73.59; H, 7.21; N, 2.86; found: C, 73.42; H, 7.28, N, 2.86%. ^{1}H NMR ($CDCl_3$) δ: 1.91 (m, 2H); 2.23 (m, 2H); 2.34 (t, $J = 7.3$, 2H); 2.60 (t, $J = 7.6$, 2H); 2.73 (t, $J = 7.3$, 1H); 2.83 (t, $J = 7.5$, 1H); 2.84 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.62 (s, 1H); 4.13 (m, 4H); 6.80–6.87 (m, 4H); 7.02–7.13 (m, 4H); 7.18–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 25.3, 29.2, 33.1, 34.8, 35.4, 35.8, 38.2, 50.6, 65.1, 114.6, 115.0, 126.2, 127.4, 127.9, 128.9, 129.7, 130.1, 139.7, 154.9, 156.4, 160.7, 177.4.

5.1.7.13. 4-[4-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy} butoxy)phenyl] butanoic acid ***6c***. Hydrolysis of **30c** [yellowish solid (2.9 g, 57%); m.p. 67–69 °C (ethyl acetate–chloroform)] afforded pure acid **6c** (2.7 g, 95%); m.p. 79–80 °C (ethyl acetate–chloroform). Anal Calcd. for $C_{31}H_{37}NO_5$ (503.6): C, 73.93; H, 7.41; N, 2.78; found: C, 73.95; H, 7.41; N, 2.73%. ^{1}H NMR ($CDCl_3$) δ: 1.70 (m, 2H); 1.96 (m, 4H); 2.40 (t, $J = 7.3$, 2H); 2.58 (t, $J = 7.4$, 2H); 2.71 (t, $J = 7.2$, 1H); 2.81 (t, $J = 7.2$, 1H); 2.85 (s, 1.5H); 2.97 (s, 1.5H); 3.44 (s, 1H); 3.46 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.2$, 1H); 3.60 (s, 1H); 4.00 (m, 4H); 6.80–6.85 (m, 4H); 7.02–7.16 (m, 4H); 7.20–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 25.2, 26.1, 33.4, 34.7, 35.4, 35.8, 38.4, 50.8, 68.7, 114.6, 114.8, 126.1, 127.3, 127.9, 128.7, 128.9, 129.6, 130.1, 139.6, 154.9, 156.3, 160.7, 177.3.

5.1.7.14. 2-Methyl-4-[4-(2-{4-[(phenethylcarbamoyl)methyl] phenoxy}ethoxy)phenyl] butanoic acid ***7a***. Hydrolysis of **31a** [yellowish glassy oil (3.1 g, 63%)] afforded pure acid **7a** (2.6 g, 86%); m.p. 121–123 °C (ethyl acetate–dichloromethane). Anal Calcd. for $C_{30}H_{35}NO_5$ (489.6): C, 73.59; H, 7.21; N, 2.86; found: C, 73.43; H, 7.27; N, 2.79%. ^{1}H NMR ($CDCl_3$) δ: 1.21 (d, $J = 7.0$, 3H); 1.70 (m, 1H); 2.00 (m, 1H); 2.48 (m, 1H); 2.60 (t, $J = 7.2$, 2H); 2.72 (t, $J = 7.4$, 1H); 2.82 (t, $J = 7.3$, 1H); 2.84 (s, 1.5H); 2.98 (s, 1.5H); 3.41 (s, 1H); 3.50 (t, $J = 7.3$, 1H); 3.60 (t, $J = 7.2$, 1H); 3.63 (s, 1H); 4.00 (m, 4H); 6.87–6.91 (m, 4H); 7.09–7.17 (m, 4H); 7.19–7.28 (m, 5H). ^{13}C NMR ($CDCl_3$): 16.7, 32.7, 32.7, 33.1, 34.8, 38.2, 40.7, 50.6, 69.3, 114.2, 114.7, 126.1, 127.3, 127.8, 128.7, 128.9, 130.1, 139.5, 154.6, 156.3, 160.7, 178.5.

5.1.7.15. 2-Methyl-4-[4-(3-{4-[(phenethylcarbamoyl)methyl] phenoxy}propoxy) phenyl] butanoic acid ***7b***. Hydrolysis of **31b** [yellowish glassy oil (2.8 g, 54%)] afforded pure acid **7b** (1.5 g, 54%); m.p. 55–59 °C (acetone–diethyl ether). Anal Calcd. for $C_{31}H_{37}NO_5$ (503.6): C, 73.93; H, 7.41; N, 2.78; found: C, 73.77; H, 7.37; N, 2.69%. ^{1}H NMR ($CDCl_3$) δ: 1.20 (d, $J = 6.9$, 3H); 1.68 (m, 1H); 2.00 (m, 1H); 2.23 (m, 2H); 2.47 (m, 1H); 2.59 (t, $J = 6.0$, 2H); 2.73 (t, $J = 6.1$, 1H); 2.84 (t, $J = 7.4$, 1H); 2.84 (s, 1.5H); 2.97 (s, 1.5H); 3.39 (s, 1H); 3.49 (t, $J = 7.3$, 1H); 3.57 (t, $J = 7.7$, 1H); 3.63 (s, 1H); 4.11 (m, 4H); 6.81–6.86 (m, 4H); 7.06–7.14 (m, 4H); 7.17–7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.6, 29.3, 32.7, 32.9, 33.1, 34.8, 38.4, 40.9, 50.7, 65.1, 114.2, 114.8, 126.1, 127.4, 127.8, 128.6, 128.9, 130.4, 139.6, 154.7, 156.3, 160.8, 178.5.

5.1.7.16. 2-Methyl-4-[4-(4-{4-[(phenethylcarbamoyl)methyl] phenoxy}butoxy)phenyl] butanoic acid ***7c***. Hydrolysis of **31c** [yellowish glassy oil (4.1 g, 77%)] afforded pure acid **7c** (3.1 g, 79%); m.p. 93–95 °C (toluene–*n*-hexane). Anal Calcd. for $C_{32}H_{39}NO_5$ (517.7): C, 74.25; H, 7.59; N, 2.71; found: C, 74.01; H, 7.74; N, 2.61%. ^{1}H NMR ($CDCl_3$) δ: 1.21 (d, $J = 7.0$, 3H); 1.70 (m, 1H); 1.95 (m, 4H); 2.01 (m, 1H); 2.48 (m, 1H); 2.60 (t, $J = 7.6$, 2H); 2.73 (t, $J = 7.2$, 1H); 2.83 (t, $J = 7.4$, 1H); 2.85 (s, 1.5H); 2.98 (s, 1.5H); 3.40 (s, 1H);

3.50 (t, $J = 7.2$, 1H); 3.60 (t, $J = 7.3$, 1H); 3.63 (s, 1H); 4.00 (m, 4H); 6.80–6.83 (m, 4H); 7.06–7.18 (m, 4H); 7.20–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.0, 16.7, 26.1, 32.7, 32.8, 33.2, 34.8, 38.1, 38.5, 40.8, 50.7, 68.7, 114.1, 126.1, 127.2, 127.9, 128.8, 130.3, 139.4, 154.6, 156.5, 160.8, 178.6.

5.1.7.17. 4-Oxo-4-[4-(2-{4-[(phenethylcarbamoyl)methyl]phenoxy]}ethoxy)phenyl] butanoic acid ***8a***. Hydrolysis of **32a** [yellowish solid (2.2 g, 44%); m.p. 91–92 °C (ethyl acetate–petrol ether)] afforded pure acid **8a** (2.0 g, 93%); m.p. 125–126 °C (ethyl acetate–diethyl ether). Anal Calcd. for $C_{29}H_{31}NO_6$ (489.6): C, 71.15; H, 6.38; N, 2.86; found: C, 71.29; H, 6.37; N, 2.85%. ^{1}H NMR ($CDCl_3$) δ: 2.76 (t, $J = 6.8$, 2H); 2.76 (t, $J = 7.3$, 1H); 2.86 (t, $J = 7.2$, 1H); 2.86 (s, 1.5H); 2.98 (s, 1.5H); 3.26 (t, $J = 6.7$, 2H); 3.40 (s, 1H); 3.50 (t, $J = 7.4$, 1H); 3.60 (t, $J = 7.2$, 1H); 3.63 (s, 1H); 4.34 (m, 4H); 6.89 (m, 2H); 6.99 (m, 2H); 7.09–7.17 (m, 2H); 7.18–7.30 (m, 5H); 7.97 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 30.7, 33.1, 34.1, 34.8, 38.3, 50.9, 69.2, 114.1, 114.8, 126.1, 127.3, 127.8, 128.3, 128.7, 129.3, 130.1, 139.7, 156.3, 160.7, 161.9, 177.5, 200.2.

5.1.7.18. 3-[4-(2-{4-[(Phenethylcarbamoyl)methyl]phenoxy}ethoxy)phenyl] prop-2-enoic acid ***9a***. Hydrolysis of **33a** [yellowish solid (2.1 g, 44%); m.p. 91–92 °C (ethyl acetate–petrol ether)] afforded pure acid **9a** (1.6 g, 78%); m.p. 151–152 °C (ethyl acetate). Anal Calcd. for $C_{28}H_{29}NO_5$ (459.5): C, 73.18; H, 6.36; N, 3.05%; found: C, 73.17; H, 6.48; N, 2.96%. ^{1}H NMR (DMSO-d_6) δ: 2.75 (t, $J = 7.3$, 2H); 2.86 (s, 1.5H); 2.92 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.2$, 1H); 3.60 (t, $J = 7.3$, 1H); 3.60 (s, 1H); 4.37 (m, 4H); 6.41 (d, $J = 16.1$, 1H); 6.95 (m, 2H); 7.06–7.17 (m, 4H); 7.19–7.25 (m, 5H); 7.64 (d, $J = 16.3$, 1H); 7.67 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 33.3, 34.8, 38.2, 50.7, 69.4, 114.1, 114.8, 115.5, 126.0, 126.8, 127.1, 127.2, 127.8, 128.7, 130.2, 139.4, 148.0, 156.4, 156.7, 160.8, 170.7.

5.1.7.19. 3-[4-(3-{4-[(Phenethylcarbamoyl)methyl]phenoxy}propoxy)phenyl] prop-2-enoic acid ***9b***. Hydrolysis of **33b** [yellowish solid (3.7 g, 76%); m.p. 94–95 °C (ethyl acetate–petrol ether)] afforded pure acid **9b** (2.1 g, 59%); m.p. 132–134 °C (aqueous ethanol). Anal Calcd. for $C_{29}H_{31}NO_5 \cdot H_2O$ (491.6): C, 70.86; H, 6.77; N, 2.85; found: C, 70.58; H, 6.47; N, 2.85%. ^{1}H NMR ($CDCl_3$) δ: 2.25 (m, 2H); 2.74 (t, $J = 7.3$, 1H); 2.84 (t, $J = 7.3$, 1H); 2.85 (s, 1.5H); 2.98 (s, 1.5H); 3.39 (s, 1H); 3.53 (t, $J = 7.4$, 1H); 3.60 (t, $J = 7.5$, 1H); 3.63 (s, 1H); 4.15 (m, 4H); 6.31 (d, $J = 16.0$, 1H); 6.84–6.94 (m, 4H); 7.11–7.26 (m, 7H); 7.48 (m, 2H); 7.73 (d, $J = 15.9$, 1H). ^{13}C NMR ($CDCl_3$) δ: 16.6, 29.3, 33.2, 34.8, 38.2, 50.6, 65.1, 114.3, 114.8, 115.7, 126.1, 126.7, 127.1, 127.7, 128.7, 130.1, 139.5, 147.9, 156.3, 156.5, 160.8, 170.5.

5.1.7.20. 3-[4-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy}propoxy)phenyl] prop-2-enoic acid ***9c***. Hydrolysis of **33c** [yellowish solid (2.7 g, 54%); m.p. 98–100 °C (toluene)] afforded pure acid **9c** (2.1 g, 82%); m.p. 145–147 °C (ethyl acetate–petrol ether). Anal Calcd. for $C_{30}H_{33}NO_5$ (487.6): C, 73.90; H, 6.82; N, 2.87; found: C, 73.66; H, 6.98; N, 2.71%. ^{1}H NMR ($CDCl_3$) δ: 1.98 (m, 4H); 2.74 (t, $J = 7.2$, 1H); 2.84 (t, $J = 7.1$, 1H); 2.86 (s, 1.5H); 2.98 (s, 1.5H); 3.40 (s, 1H); 3.54 (t, $J = 7.1$, 1H); 3.60 (t, $J = 7.4$, 1H); 3.63 (s, 1H); 4.07 (m, 4H); 6.31 (d, $J = 15.9$, 1H); 6.83–6.93 (m, 4H); 7.11–7.28 (m, 7H); 7.48 (m, 2H); 7.73 (d, $J = 15.9$, 1H). ^{13}C NMR ($CDCl_3$) δ: 16.0, 26.0, 33.1, 34.8, 38.2, 50.6, 68.9, 114.2, 114.7, 115.5, 126.0, 126.7, 127.2, 127.3, 127.8, 128.7, 130.1, 139.5, 148.1, 156.3, 156.7, 160.8, 170.5.

5.1.7.21. 3-[3-Methoxy-4-(2-{4-[(phenethylcarbamoyl)methyl]phenoxy}ethoxy)phenyl] prop-2-enoic acid ***10a***. Hydrolysis of **34a** [yellowish solid (2.5 g, 50%); m.p. 101–102 °C (ethyl acetate)] afforded pure acid **10a** (2.2 g, 91%); m.p. 120–123 °C (ethyl acetate). Anal Calcd. for $C_{29}H_{31}NO_6$ (489.6): C, 71.15; H, 6.38; N, 2.86; found: C, 71.28; H, 6.47; N, 2.75%. ^{1}H NMR ($CDCl_3$) δ: 2.75 (t, $J = 7.3$, 2H); 2.86 (s, 1.5H); 2.92 (s, 1.5H); 3.38 (s, 1H); 3.50 (t, $J = 7.2$, 1H); 3.57 (t, $J = 7.4$, 1H); 3.58 (s, 1H); 3.82 (s, 3H); 4.33 (m, 4H); 6.43 (d, $J = 16.0$, 1H); 6.91–6.95 (m, 2H); 7.01–7.10 (m, 3H); 7.16–7.34 (m, 7H); 7.57 (d, $J = 16.1$, 1H). ^{13}C NMR ($CDCl_3$): 33.2, 35.0, 38.4, 50.6, 56.1, 69.3, 69.7, 111.1, 114.8, 115.2, 119.2, 126.0, 127.4, 127.9, 128.7, 130.2, 139.5, 145.7, 147.9, 149.8, 156.3, 160.8, 170.5.

5.1.7.22. 3-[3-Methoxy-4-(3-{4-[(phenethylcarbamoyl)methyl]phenoxy}propoxy)phenyl] prop-2-enoic acid ***10b***. Hydrolysis of **34b** [yellowish solid (4.8 g, 94%); m.p. 86–88 °C (ethyl acetate–petrol ether)] afforded pure acid **10b** (2.6 g, 55%); m.p. 129–132 °C (ethyl acetate). Anal Calcd. for $C_{30}H_{33}NO_6$ (503.6): C, 71.55; H, 6.61; N, 2.78; found: C, 71.62; H, 6.61; N, 2.71%. ^{1}H NMR ($CDCl_3$) δ: 2.31 (m, 2H); 2.74 (t, $J = 7.4$, 1H); 2.84 (t, $J = 7.6$, 1H); 2.85 (s, 1.5H); 2.98 (s, 1.5H); 3.40 (s, 1H); 3.53 (t, $J = 7.8$, 1H); 3.60 (t, $J = 7.6$, 1H); 3.62 (s, 1H); 3.88 (s, 3H); 4.20 (m, 4H); 6.31 (d, $J = 15.9$, 1H); 6.84–6.87 (m, 3H); 7.04–7.14 (m, 4H); 7.18–7.28 (m, 5H); 7.65 (d, $J = 16.1$, 1H). ^{13}C NMR ($CDCl_3$) δ: 29.1, 33.1, 34.8, 38.3, 50.6, 56.1, 65.3, 65.6, 111.1, 114.8, 115.4, 115.6, 119.1, 126.0, 127.3, 127.8, 128.6, 130.1, 139.4, 145.7, 149.8, 156.3, 160.7, 170.5.

5.1.7.23. 3-[3-Methoxy-4-(4-{4-[(phenethylcarbamoyl)methyl]phenoxy}butoxy)phenyl] prop-2-enoic acid ***10c***. Hydrolysis of **34c** [yellowish solid (5.2 g, 98%); m.p. 71–73 °C (ethyl acetate–petrol ether)] afforded pure acid **10c** (3.5 g, 69%); m.p. 116–117 °C (acetone–diethyl ether). Anal Calcd. for $C_{31}H_{35}NO_6$ (517.6): C, 71.93; H, 6.82; N, 2.71; found: C, 71.81; H, 6.82; N, 2.71%. ^{1}H NMR ($CDCl_3$) δ: 2.01 (m, 4H); 2.75 (t, $J = 7.5$, 1H); 2.83 (t, $J = 7.5$, 1H); 2.87 (s, 1.5H); 2.98 (s, 1.5H); 3.40 (s, 1H); 3.51 (t, $J = 7.7$, 1H); 3.60 (t, $J = 7.6$, 1H); 3.63 (s, 1H); 3.88 (s, 3H); 4.02 (m, 2H); 4.13 (m, 2H); 6.31 (d, $J = 15.8$, 1H); 6.84–6.86 (m, 3H); 7.04–7.15 (m, 4H); 7.17–7.29 (m, 5H); 7.71 (d, $J = 15.9$, 1H). ^{13}C NMR ($CDCl_3$) δ: 25.9, 33.3, 34.8, 38.2, 50.6, 56.1, 68.8, 69.2, 111.2, 114.9, 115.2, 115.6, 119.1, 126.2, 127.1, 127.7, 128.4, 130.1, 139.4, 145.7, 148.0, 149.8, 156.3, 160.8, 170.5.

*5.1.7.24. 2-[7-(3-{4-[(Phenethylcarbamoyl)methyl]phenoxy} propoxy)naphthyl] propanoic acid **11b***. Hydrolysis of **35b** [white precipitate (4.3 g, 80%); m.p. 92–95 °C (ethyl acetate–petrol ether)] afforded pure acid **11b** (2.7 g, 64%); m.p. 105–106 °C (ethyl acetate–diethyl ether). Anal Calcd. for $C_{33}H_{35}NO_5$ (525.6): C, 75.40; H, 6.71; N, 2.66; found: C, 75.45; H, 6.79; N, 2.53%. ^{1}H NMR ($CDCl_3$) δ: 1.57 (d, $J = 7.2$, 3H); 2.30 (m, 2H); 2.71 (t, $J = 7.1$, 1H); 2.81 (t, $J = 7.2$, 1H); 2.82 (s, 1.5H); 2.96 (s, .5H); 3.39 (s, 1H); 3.47 (t, $J = 7.1$, 1H); 3.58 (t, $J = 7.3$, 1H); 3.61 (s, 1H); 3.87 (q, $J = 7.2$, 1H); 4.15 (m, 2H); 4.26 (m, 2H); 6.83 (m, 2H); 7.00–7.32 (m, 10H); 7.63–7.68 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 16.2, 29.0, 33.2, 34.8, 38.3, 43.2, 50.6, 65.1, 105.3, 114.8, 118.5, 126.0, 126.2, 126.7, 127.4, 127.9, 128.5, 128.7, 129.1, 129.4, 130.2, 132.7, 133.0, 139.6, 156.1, 156.5, 160.7, 177.3.

*5.1.7.25. 2-[7-(4-{4-[(Phenethylcarbamoyl)methyl]phenoxy} butoxy)naphthyl] propanoic acid **11c***. Hydrolysis of **35c** [white precipitate (2.6 g, 47%); m.p. 110–111 °C (ethyl acetate)] afforded pure acid **11c** (2.4 g, 95%); m.p. 152–153 °C (ethyl acetate). Anal Calcd. for $C_{34}H_{37}NO_5$ (539.66): C, 75.67; H, 6.91; N, 2.60; found: C, 75.49; H, 2.91; N, 2.57%. ^{1}H NMR ($CDCl_3$) δ: 1.52 (d, $J = 7.1$, 3H); 2.02 (m, 4H); 2.76 (t, $J = 7.2$, 1H); 2.80 (t, $J = 7.2$, 1H); 2.90 (s, 1.5H); 2.93 (s, 1.5H); 3.33 (s, 1H); 3.54 (t, $J = 7.3$, 1H); 3.58 (t, $J = 7.4$, 1H); 3.65 (s, 1H); 3.78 (q, $J = 7.1$, 1H); 4.04 (m, 2H); 4.14 (m, 2H); 6.83 (m, 2H); 7.00 (d, $J = 7.6$, 1H); 7.07–7.27 (m, 8H); 7.37 (d, $J = 7.6$, 1H); 7.61–7.66 (m, 3H). ^{13}C NMR ($CDCl_3$) δ: 16.2, 26.0, 33.1, 34.8, 38.5, 43.1, 50.6, 68.7, 105.3, 114.8, 118.5, 126.0, 126.2, 126.7, 127.3, 127.7, 128.4, 128.9, 129.1, 129.5, 130.1, 132.7, 133.2, 139.6, 156.1, 156.3, 160.7, 177.5.

5.2. Evaluation of lipophilicity

The values of log *P* were calculated using the KOWWIN program, version 1.63 (Syracuse Research Corp., U.S.A.).

Evaluation of lipophilicity by the HPLC method [19]. Experiments were carried out using a liquid chromatograph with an LCP 4100 pump (Ecom, Prague, Czech Republic), autosampler Waters 717 plus, UV detector Waters 486 (Waters Assoc., Milford, MA, U.S.A.) and data module CSW (DataApex, CR). Thermoquest Hypersil ODS 5 μm (Thermo Hypersil-Keystone, Asmoor Runcorn, GB) in a 250 × 4.6 mm I.D. column was used as a stationary phase and the mixture of acetonitrile and pH 5.75 buffer (1:1) was used as a mobile phase. Detection was performed by UV absorption at 233 nm. The retention time of sodium nitrate (0.02% solution) was taken as t_0 and the capacity factor k was evaluated from the retention time of the solute, t_R, by the relationship: $k = (t_R - t_0)/t_0$.

5.3. Quantitative structure–activity analysis

The regression equations were calculated using Statgraphics Program, U.S. Version 4 (STSC Inc. U.S.A.).

The coefficients in the regression equations were calculated from experimental results by multiple regression analysis and their statistical significance was tested with the Student's *t*-test. Statistical significance of regression equations was tested by standard deviations (*s*), coefficients of multiple correlations (*r*) and the Fisher–Snedecor criterion (*F*). The statistical significance level *p* was better than 0.005 for both the whole equations and individual variables with the exceptions mentioned in the text.

5.4. Biological evaluation

The production of LTB_4 was determined in rat polymorphonuclear cells from the pleural exudate elicited by heat-inactivated rat serum [39,40]. The cells were stimulated with Ca^{2+} ionophore A23187 (Sigma) and incubated with various concentrations of the test compounds. LTB_4 was determined using a commercial RIA kit (Amersham). The *in vitro* activity was expressed in concentration C (μM) causing 50% inhibition of LTB_4 biosynthesis. Six points at different concentrations were used for the calculation of C.

Inhibition of carrageenan edema was evaluated by the method of Winter [41], the experimental conditions are described elsewhere [42]. The effect was expressed as percentage inhibition after a dose of 100 mg/kg in comparison with untreated control. Arachidonic acid-induced ear inflammation in mice was performed by the method of Opas et al. [43], the ear pinna inflammation was induced by application of 20 μl of arachidonic acid solution in acetone. The compound was given orally (200 mg/kg) 1 h before edema induction. The degree of ear hyperemia and the weight of ear were evaluated 1 h after application of arachidonic acid. The results were expressed as percentage inhibition relative to untreated control. Ulcerative colitis in mice [44] was induced by addition of 3% dextrane disodium sulfate into drinking water to BALB/c mice of 20 g average weight for 7 days. The compound was given in the dose of 250 mg/kg 1 h before induction of ulcerative colitis. This dosage was chosen to be comparable with sulfasalazine used as a standard. Colitis was evaluated clinically (loss of weight, rectal prolapse, blood in stool, stool consistency), pathologically (colonic bleeding, length of colon) as the ratio of diseased and total number of animals or as percentage of control, and histologically (0–3 score). Colon descendens was fixed in 5% formalin and embedded in paraffin for histologic evaluation. Sections were stained with hematoxylin/eosin. Four transversal sections were evaluated, each obtained at 500 μm distance. The microscopic findings were assessed semiquantitatively and weighted score for each section was obtained, ranging from 0 (no signs of colitis) to 3 (severe colitis). The histological grade consists mainly of the extent of ulceration, inflammatory infiltration and edema of the colon wall corrected with minor criteria (e.g. presence of the leucocytes in lumen, extent of the dilatation of the crypts). Mice were scored individually, each score representing the mean of four sections. The compounds were administered in 0.5% aqueous solution of (carboxymethyl)cellulose in all three *in vivo* tests.

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