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Synthesis of carboxylated flavonoids as new leads for LTD_4 antagonists

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Summary — A series of 3'- and 5'-carboxylated chalcones, 6- or 8-carboxylated flavones and 6-carboxylated flavanones, -flavanols and -flavans were prepared. The compounds were tested for their inhibitory activities against leukotriene D_4 (LTD_4) induced contraction of guinea-pig ileum. A new and convenient synthetic route to 3-acetyl-2-hydroxybenzoic acid (**1d**), a key intermediate for the synthesis of 3'-carboxy-2'-hydroxychalcones and 8-carboxylated flavones, was developed. The activities of the tested compounds ranged from 0 to 63% inhibition at 10^{-5} M drug concentration against a single challenge of 10^{-8} M LTD_4. Several compounds were tested in a radioligand binding assay against [^{3}H]LTD_4 on guinea-pig lung membrane. The quinoline-containing chalcone **12** and flavone **17** were found to exhibit significant but weak affinities for LTD_4 receptors with pK_D-values of 4.95 and 4.83, respectively, and are interesting lead structures for the development of rigid LTD_4 antagonists. In contrast, the rest of the compounds tested in the binding assay did not show significant displacement of the radioligand, implying that for these compounds the functional activity is probably not caused by competitive antagonism at the LTD_4 receptor. The exact mechanism of the relaxant activity remains unclear.

carboxylated flavonoid / leukotriene D_4 antagonist / antiasthmatic agent

Introduction

Flavonoids bearing carboxylic acid substituents are compounds with interesting pharmacological properties [1]. Besides anticancer effects [2, 3], spasmolytic properties [4–6], retinoidal effects [7] and inhibition of histamine-induced gastric acid secretion [8], several carboxylated flavonoids have been found to possess antianaphylactic properties [9–13]. For example, 6-carboxyflavone and several derivatives display anti-allergic activity comparable to that of disodium cromoglycate [10, 14] in the passive cutaneous anaphylactic (PCA) reaction in the rat [13]. Investigation of structure–activity relationships on these flavones suggests that an acidic moiety, a planar molecular arrangement and a direct connection of the acidic moiety to the aromatic nucleus are important structural features for antianaphylactic properties.

In our search for novel and preferentially rigid leukotriene D_4 (LTD_4) antagonists, which are promising candidates for a new generation of antiasthma drugs [15–19], we became interested in the antianaphylactic activities of the carboxylated flavones. The known structure–activity relationships of LTD_4 receptor antagonists [21–23] coincide with those of antianaphylactic carboxylated flavones in that a flat unit (mimicking the triene system of LTD_4), and an acidic moiety (mimicking the carboxyl of LTD_4) are involved in the interaction with the LTD_4 receptor. Since LTD_4 is the most potent constituent of SRS-A (slow reacting substance of anaphylaxis) we speculated that the mode of action of antianaphylactic flavones [13] could be by antagonism at the LTD_4 receptor.

In this paper we report the synthesis and LTD_4-inhibitory activity of a new series of carboxylated flavones, chalcones, flavanones, flavanols and flavans (fig 1). We also prepared some quinolinyl analogues, which would give highly rigid structures closely resembling the existing LTD_4 antagonists Wy 48252 [20] and compound **A**, which was prepared by researchers at Rorer [21] (scheme 1).

Chemistry

The syntheses of flavones **13–21** were carried out by the routes depicted in scheme 2. *Method A* involves the formation of chalcones **2–12** by the Claisen–Schmidt condensation of an aromatic aldehyde with acetophenones **1a–d** [22].

Abbreviations. LTD_4: leukotriene D_4.

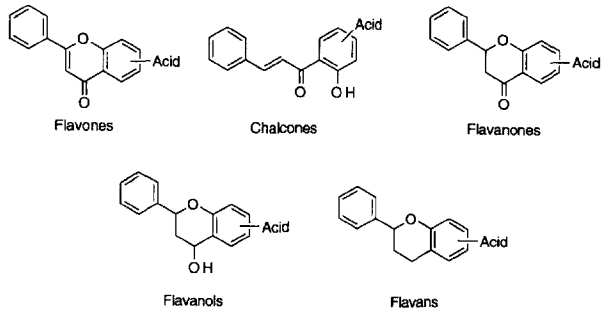
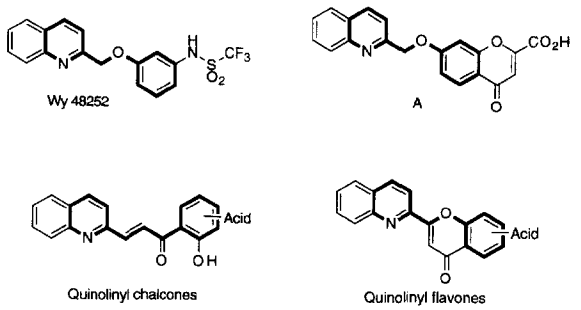
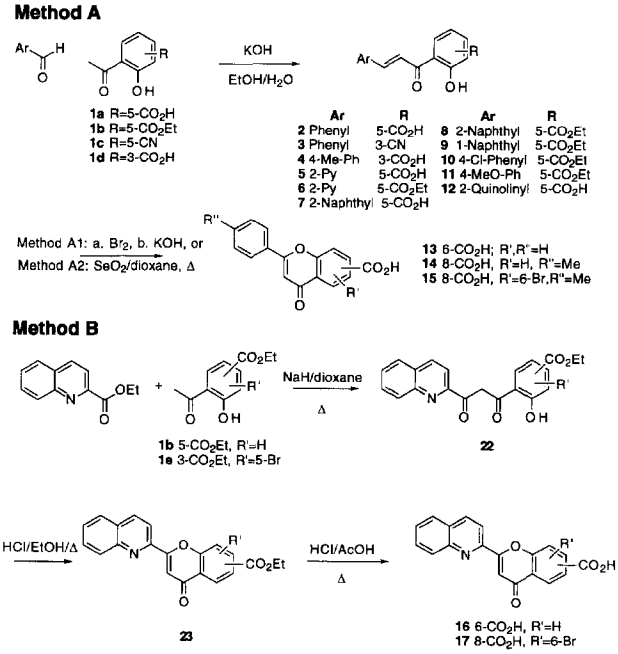


Fig 1. Structures of target flavonoids.



Scheme 1. Structural similarities between quinoline containing flavonoids of this study with the known LTD_4 antagonists.

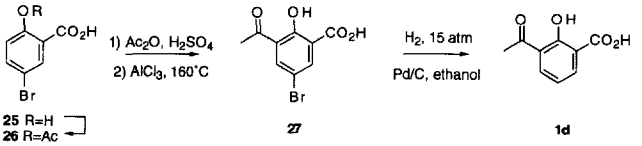
Chalcones **2** and **4** were converted to flavones by an oxidative ring closure either with bromine and a base [8, 23] giving **13** and **15**, or by refluxing with SeO_2 in dioxane yielding **14** [24]. In the reaction of **4** with bromine, besides addition of bromine to the chalcone double bond, bromination of the aromatic ring at the 5'-position occurred, resulting in **15**. Ring closure of **4** with SeO_2 gave **14** without further side reactions. The condensation of the benzoic acid derivatives **1a**, **1b** and **1d** with quinoline-2-carboxaldehyde proved to be troublesome. Instead of the yellow crystals normally isolated, mixtures of products were obtained, from which the desired chalcones could not be purified. The same was found for the condensation of **1b** with pyridine-4-carboxaldehyde. Claisen–Schmidt condensation of quinoline-2-carboxaldehyde with **1a** via the method of Hsu [25] gave **12** as an orange solid in only 5% yield. *Method B* was used for the preparation of the quinoline-containing flavones **16** and **17**. Claisen condensation of **1b** or **1e** with quinaldic ester (scheme 2B) yielded β-diketones **22** which were subsequently converted to the flavones **23** by an acid-



Scheme 2. Synthetic scheme of chalcones and flavones.

catalysed ring closure. Hydrolysis of the flavone esters by heating in acetic acid with hydrochloric acid yielded the desired flavones [13].

The starting acetophenones **1a–c** were synthesized by Fries rearrangement of the corresponding acetates [10, 13]. Existing synthetic routes to **1d** involve either Lewis-acid-catalysed cycloaromatization [26] or a tedious oxidation of 3-allyl-2-hydroxyacetophenone [27, 28]. We developed a new straightforward synthetic route to **1d** (scheme 3) which is analogous to the preparation of **1a–c**, in that the acyl group is introduced by means of a Fries rearrangement. Since the Fries rearrangement of acetyl salicylic acid predominantly yields the *para*-acetylated product [29], the protection of the *para* position [30] is necessary in order to selectively introduce the acyl group into the *ortho* position. Use of *t*-butyl as a positional protec-

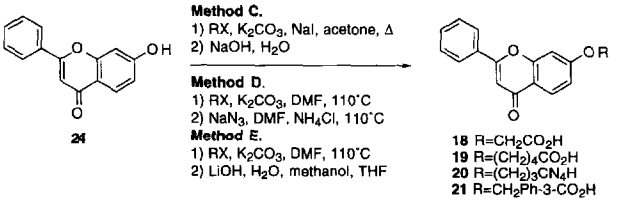


Scheme 3. Synthesis of **1d**.

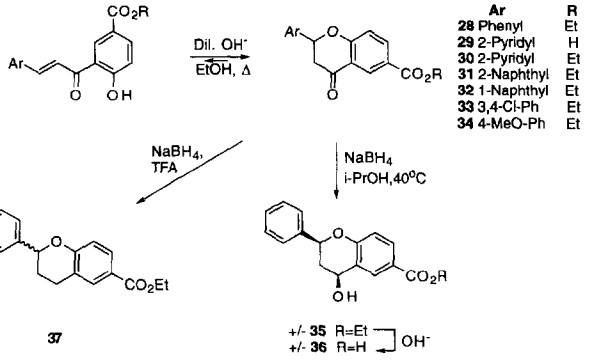
tive group proved unsuitable, because its removal failed under either acidic [31] or transalkylation conditions [32], although it could easily be introduced by Friedel–Crafts alkylation of methyl salicylate. We chose bromine as the protective group. Commercially available 5-bromosalicylic acid **25** was acetylated and Fries rearrangement of **26** could be achieved on a 100 g scale to give **27** in 36% yield. Removal of bromine was achieved by a selective reduction with hydrogen on palladium catalyst, giving **1d** in 31% overall yield. Refluxing of **27** in a solution of 5% sulphuric acid in ethanol afforded the corresponding ester **1e**.

A series of 7-substituted flavones **18–21** were prepared to investigate the influence of the chain length between the acidic function and the aromatic nucleus. Flavones **18–21** were obtained by alkylation of 7-hydroxyflavone [33] **24** with ethyl α-chloroacetate, ethyl-4-bromovalerate, 4-bromobutyronitrile and ethyl 3-bromomethylbenzoate (scheme 4). With ethyl 3-bromomethylbenzoate and ethyl α-chloroacetate the alkylation was performed by refluxing the reactants in acetone in the presence of one equivalent of potassium carbonate and sodium iodide *(Method C)*. Hydrolysis of the corresponding esters yielded **18** and **21**. For the non-activated halogenides, eg, 4-bromobutyronitrile and ethyl 4-bromovalerate, the alkylation was performed in DMF with potassium carbonate at 110 °C, followed by reaction with sodium azide *(Method D)* or hydrolysis *(Method E)* to form the tetrazole **20** or the carboxylic acid **19** respectively.

A series of higher saturated flavonoids was prepared according to the routes depicted in scheme 5. Flavanones **28–34** were prepared by intramolecular Michael addition of the 2'-hydroxychalcones [23]. This equilibrium reaction was shifted predominantly to the flavanones by refluxing in ethanol under dilute basic conditions. From the resulting mixtures of flavanone and traces of chalcone, the products could be purified either by column chromatography or crystallization for **29**. Reduction of flavanone **28** with sodium borohydride in isopropanol yielded flavanol **35** as a single diastereomer. With NOE-difference spectroscopy (400 MHz) a *cis*-configuration was assigned to this compound; NOE-interactions between H2 (δ 5.26 ppm) and H4 (δ 5.14 ppm) were observed. Hydrolysis of **35** yielded the corresponding acid **36**. Reduction of **28** with sodium borohydride in trifluoroacetic acid yielded flavan **37**. Reduction of **34** under the above conditions did not succeed, because the flavanone was converted back to chalcone **11**. This effect can be ascribed to the electron-donating effect of the methoxy substituent which stabilizes a positive charge on C3, thereby stimulating ring opening towards the chalcone.



Scheme 4. Synthesis of 7-substituted flavones **18–21**.



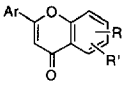
Scheme 5. Synthesis of 6-carboxylated flavanones, flavanols and flavans **28–37**.

Results and discussion

All compounds shown in tables I–III were tested for their inhibitory activities of LTD_4-induced contraction of guinea-pig ileum. The known LTD_4 receptor antagonist FPL 55712 [34] was taken as a reference. In table I the results obtained for the flavones **13–21** are summarised. Surprisingly, compound **13**, which was reported to have good PCA-activity [13], does not inhibit the LTD_4-induced smooth muscle contraction. The 8-carboxylated flavones **14** and **15** showed a slight inhibition, as did the quinoline analogue **16**. Flavones **18–21** also inhibited the contraction of the ileum with **21** showing the highest activity. In a binding assay on guinea-pig lung tissue [35] only compound **17** displaced [^{3}H]LTD_4 from the LTD_4 receptor with a pK_D-value of 4.83. Except for **17**, the antagonistic effects measured in the functional assay are not caused by competitive antagonism at the level of the LTD_4 receptor.

The chalcones depicted in table II show LTD_4 antagonistic activities in the functional assay with a comparable level of activity; compound **9** is however completely inactive and compound **7** shows a rela-

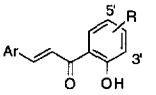
Table I. LTD_4 inhibitory activity of 6- , 7- and 8-substituted flavones and some heterocyclic derivatives.



Compound	*Ar*	*R*	*R'*	*Method of preparation*	*% Inhibition at 10^{-5} M*[a]	*pK_D*[b]
13	Phenyl	6-CO_2H	H	A1	0	
14	4-Me-Phenyl	8-CO_2H	H	A2	20 ± 9	
15	4-Me-Phenyl	8-CO_2H	6-Br	A1	16 ± 14	
16	2-Quinolinyl	6-CO_2H	H	B	31 ± 13	ND
17	2-Quinolinyl	8-CO_2H	6-Br	B	15 ± 7	4.83
18	Phenyl	7-OCH_2CO_2H	H	C	12 ± 2	ND
19	Phenyl	7-$O(CH_2)_4CO_2H$	H	E	35 ± 10	ND
20	Phenyl	7-$O(CH_2)_3CN_4H$	H	D	23 ± 4	ND
21	Phenyl	7-OCH_2Ph-3-CO_2H	H	C	63 ± 9	ND
FPL 55712			H		100	5.95

ND: no dissociation. [a]% Inhibition of the LTD_4-induced contraction of guinea-pig ileum was measured at a drug concentration of 10^{-5} M, against a single LTD_4 concentration of 10^{-8} M. Data are means of three independent determinations. FPL 55712 was taken as reference, at the same concentration. [b]Binding assay was performed as the displacement of [^{3}H]LTD_4 from guinea-pig lung membrane fractions by a drug at concentrations of 10^{-9} to 10^{-4} M.

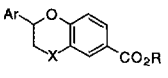
Table II. LTD_4 inhibitory activity of 3'- and 5'-carboxy-2'-hydroxychalcones and some heterocyclic derivatives.



Compound	*Ar*	*R*	*% Inhibition at 10^{-5} M*[a]	*pK_D*[b]
2	Phenyl	5'-CO_2H	20 ± 16	
3	Phenyl	5'-CN	52 ± 3	
4	4-Me-Phenyl	3'-CO_2H	33 ± 19	
5	2-Pyridyl	5'-CO_2H	23 ± 10	
6	2-Pyridyl	5'-CO_2Et	25 ± 6	
7	2-Naphthyl	5'-CO_2H	72 ± 4	ND
8	2-Naphthyl	5'-CO_2Et	20 ± 11	ND
9	1-Naphthyl	5'-CO_2Et	0	
10	4-Cl-Phenyl	5'-CO_2Et	17 ± 6	
11	4-MeO-Phenyl	5'-CO_2Et	18 ± 4	
12	2-Quinolinyl	5'-CO_2H	29 ± 9	4.95
FPL 55712			100	5.95

[a,b]See table I.

Table III. LTD_4 inhibitory activity of 6-carboxylated flavanones, flavanols and flavans and some heterocyclic derivatives.



Compound	*Ar*	*X*	*R*	*% Inhibition at 10^{-5} M*[a]	*pK_D*[b]
28	Phenyl	CO	Et	15 ± 14	ND
29	2-Pyridyl	CO	H	17 ± 4	
30	2-Pyridyl	CO	Et	29 ± 12	
31	2-Naphthyl	CO	Et	26 ± 16	
32	1-Naphthyl	CO	Et	19 ± 15	
33	3,4-Cl-Phenyl	CO	Et	21 ± 3	
34	4-MeO-Phenyl	CO	Et	18 ± 13	
35	Phenyl	CHOH	Et	59 ± 19	ND
36	Phenyl	CHOH	H	13 ± 12	
37	Phenyl	CH_2	Et	36 ± 15	ND
FPL 55712				100	5.95

[a,b]See table I.

tively high activity. It is noteworthy that there is no clear difference in activity between the carboxylic acids and their corresponding esters or nitriles, in contrast to the structure–activity relationships found both for the antianaphylactic activity of the 6-carboxylic flavones [12, 13] and for the LTD_4 antagonists [36]. The same can be seen in table III, in which the flavanones **28–34** and flavanols **35–36** and flavan **37** are shown. Here again inhibitions of about 20% at 10^{-5} M are found for most compounds; the non-acidic **35** shows even higher inhibition than its acidic analogue **36**. Binding assay of a selected number of these flavonoids revealed only the quinoline containing chalcone **12** as a competitive LTD_4 antagonist with a pK_D-value of 4.95.

Because all series of compounds with different structural features show the activities in the same range, no structure–activity relationships can be elucidated. The planarity and the presence and position of an acidic functionality are not crucial features for the LTD_4 antagonistic activities observed in the functional assay. To test the specificity for LTD_4 of the observed relaxant activity we also tested compounds **3**, **7**, **16** and **35** in the same functional assay against a single challenge of 10^{-6} M histamine. In this case no significant inhibition of the smooth muscle contraction was found, implying that the activity is somehow related to the signal transduction of LTD_4.

With compounds **12** and **17** we have found two new compounds with significant but weak competitive LTD_4-antagonistic activities, compound **17** being highly rigid. Comparison of **12** and its naphthyl analogue **7** shows importance of the quinoline. Similar results were obtained for other quinoline-containing LTD_4 antagonists [21, 37–39]. The lack of receptor affinity of compound **16** indicates that, again similar to results described in literature [20, 40], the relative arrangement of the quinoline and the acidic moiety are important for activity. As the carboxylic group of the active chalcone **12** most likely overlaps the 8-COOH of **17**, but not the 6-COOH of **16**, we conclude that the important structural feature for receptor affinity of the flavone **17** is the 8-COOH rather than the bromine at the 6-position.

Conclusions

Almost all tested flavonoids possess relaxant activities on LTD_4-induced contraction of guinea-pig ileum. Only the quinoline-containing flavonoids **12** and **17** appear to be competitive antagonists of the LTD_4 receptor. Although for the other compounds some specificity for LTD_4 is observed, the exact mechanism of action remains unclear. Investigation of other properties, such as antioxidant actions which are already known for several naturally occurring flavonoids [41, 42], might give a clearer picture of the mechanism of action of these compounds.

With **12** and **17** we have found two structurally new LTD_4 antagonists, which could be useful leads for the development of new LTD_4 antagonists. Structure–

activity relationships show the importance of the quinoline moiety and the presence and position of an acidic moiety. Taking into account the structural simplicity and the rigidity, these compounds, especially **17**, may be useful for gaining a better understanding of the LTD_4 receptor–antagonist interactions.

Experimental protocols

Pharmacology

Male guinea pigs (300–350 g) were killed by a sharp blow to the head. A segment of ileum was removed and cut into segments of approximately 1 cm. Each segment was tied to a holder and attached to a transducer by means of a thread, leaving the lumen open. The ilea were then transferred to 20 mL organ baths containing Krebs buffer and equilibrated for 1 h. After stabilization, the ileum was challenged with a single dose of 10^{-8} M LTD_4, and the contraction was recorded. After washing for 0.5 h the process was repeated once to examine the reproducibility. The ileum was then incubated with a 10^{-5} M drug concentration for 0.5 h. The contraction in the presence of the drug was recorded and after washing out the ligand another single dose of 10^{-8} M LTD_4 was given to see if the maximum was reached again. Inhibition by the drug is expressed as percentage of the decrease of the contraction in the presence of the drug over the maximum contraction without the drug. Each compound was tested on segment of ileum from three different guinea pigs. The results are depicted in tables I–III.

For the binding assay a literature procedure was used [35].

Chemistry

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AC (200 MHz, FT) (standard) or a Bruker (400 MHz) spectrometer when stated, with tetramethylsilane as an internal standard at room temperature, unless otherwise stated. The multiplicity of the carbon signals was determined by DEPT or APT spectra, the symbols used are (q) for primary, (t) for secondary, (d) for tertiary and (s) for quaternary carbon signals. NOE-difference spectra and coupled carbon spectra were recorded on a Bruker 400 MHz. High resolution mass spectra were recorded on a Finnigan MAT-90. Melting points were measured on a Mettler FP-5 + FP-52 apparatus equipped with a microscope and are uncorrected. The physical data of the tested compounds are summarised in tables IV–VI.

Synthesis of 3-acetyl-2-hydroxybenzoic acid ***1d***

To a well-stirred mixture of 100 g (0.46 mol) of 5-bromosalicylic acid and 105 mL acetic anhydride 0.5 mL concentrated H_2SO_4 was added. After a few minutes the reaction mixture solidified and was suspended in water (1000 mL). The solid was filtered and washed with water. The white solid was dissolved in ethyl acetate (1000 mL), washed with brine (2 x 300 mL) and dried over Na_2SO_4. Evaporation of the solvent yielded 105 g (0.41 mol) 2-acetyloxy-5-bromobenzoic acid **26** as white crystals. Yield 88%; ^{1}H-NMR (DMSO) δ 2.26 (s, 3H, CH_3CO_2Ar), 7.20 (d, 1H, ^3J = 8.6 Hz, H_3), 7.84 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.6 Hz, H4), 8.03 (d, 1H, ^4J = 2.6 Hz, H6). ^{13}C-NMR (DMSO); δ 20.51 (q), 117.87 (s), 125.93 (s), 125.96 (d), 133.38 (d), 136.18 (d), 149.11 (s), 164.15 (s), 168.83 (s).

5-Bromoacetylsalicylic acid (100 g, 0.39 mol), and $AlCl_3$ (159 g, 1.20 mol) were mixed in a 3000 mL three-necked flask and heated to 160 °C under mechanical stirring. After 3 h the reaction mixture was cooled to room temperature, powdered in a mortar and poured onto 800 g ice containing 200 mL concentrated HCl. The slurry was extracted with ethyl acetate (3 x 350 mL), washed with 1 N HCl (3 x 200 mL) and brine (400 mL) and dried over Na_2SO_4. After evaporation of the solvent the crude product was washed with dichloromethane to remove the side products. After filtration and drying 36.4 g (0.14 mol) of **27** was obtained as a pale brown powder. Yield 36%; mp 200.1 °C; ^{1}H-NMR (DMSO) δ 2.59 (s, 3H, CH_3CO), 7.92 (d, 1H, ^4J = 2.7 Hz, H4), 8.01 (d, 1H, ^4J = 2.7 Hz, H6), 11.64 (br, s, 2H, ArOH, $ArCO_2H$). ^{13}C-NMR (DMSO); δ 30.62 (q), 109.36 (s), 117.11 (s), 127.46 (s), 136.52 (d), 137.21 (d), 159.76 (s), 169.94 (s), 197.18 (s).

Compound **27** (10.0 g, 38.6 mmol) was dissolved in 75 mL ethanol. After addition of 1.0 g 10% Pd/C the reaction mixture was hydrogenated under 15 atm H_2-pressure at room temperature for 2 h. The catalyst was filtered, the solution was neutralized with 2 N NaOH. After removal of the solvent the off-white solid was dissolved in 1 N NaOH and precipitated by adding 3 N HCl to remove the salts. **1d** (6.8 g, 37.7 mmol, 98%) was obtained as a white solid, which could be recrystallized from water; mp 131.8–133.0 °C (lit: 135–136 °C [27]); ^{1}H-NMR (DMSO); δ 2.63 (s, 3H, CH_3COAr), 7.03 (t, 1H, ^3J = 7.8 Hz, H5), 7.94 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.8 Hz, H4), 8.03 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.8 Hz, H6). ^{13}C NMR (DMSO) δ 30.58 (q), 114.92 (s), 118.53 (d), 125.44 (s), 135.18 (d), 135.62 (d), 160.82 (s), 171.07 (s), 198.74 (s). HRMS *m/e* (M^+) Calc for $C_9H_8O_4$ 180.0423. Found 180.0419 ± 0.0006.

General procedure for ethyl esters of 5'-carboxylic chalcones

A mixture of equimolar amounts of an aromatic aldehyde and ethyl 3-acetyl-4-hydroxybenzoate **1b** was dissolved in 5% KOH/ethanol and was stirred at room temperature for 3–7 days until TLC (dichloromethane or ethyl acetate/petroleum ether 1:10) showed completion of the reaction. The reaction mixture was poured onto ice and acidified with 3 N HCl. The precipitate was either filtered, or extracted with ethyl acetate, washed with brine, dried over sodium sulphate and evaporated. The crude products were recrystallized from ethanol yielding yellow crystalline solids.

General procedure for 5'-carboxylic acid chalcones and 5'-cyano chalcones

A mixture of equimolar amounts of an aromatic aldehyde and 3-acetyl-4-hydroxybenzoic acid **1a** or benzonitril **1c** were dissolved in 25 mL ethanol. After addition of the same volume of 25% NaOH solution in water the reaction mixture was stirred for several days until completion (TLC; ethyl acetate/petroleum ether 40-60/acetic acid (2:20:1)). Neutralization and filtration yielded the crude products which were recrystallized from ethanol, ethanol/THF or ethanol/DMF (tables IV–VI) to yield the chalcones as yellow precipitates.

General procedures for the preparation of flavones

Method A1. To a solution of 10 mmol chalcone in 50 mL acetic acid, 1.75 g (11 mmol) bromine was slowly added. After stirring the mixture overnight, 100 mL of 1% $NaHSO_3$ in water was added. The precipitate was filtered and resuspended in 50 mL ethanol and 5 mL 20% KOH in water was added. After stirring for another 2 h the reaction mixture was acidified and the solid was filtered. Recrystallization from ethanol (**13**) or ethanol/DMF (**15**) yielded the pure flavones.

Method A2. A mixture of 2.43 g (8.62 mmol) of **4** and 2.5 g SeO_2 (22.5 mmol) and 2 mL DMSO were refluxed in 50 mL dioxane for 1 h. The black solid was filtered and the dioxane was removed in vacuo. The remaining oil was suspended in 10 mL water and filtered. Recrystallization from ethanol yielded 1.42 g (5.07 mmol, 59%) **14** as an off-white solid.

Method B. Quinaldic ethyl ester (3.2 g, 16 mmol) and 12 mmol **1b** or **1e** were dissolved in 50 mL dioxane, the solution was added to a suspension of 1.92 g (48 mmol) NaH (60% dispersion in oil) in 20 mL dioxane. After refluxing for 4 h, 70 mL of petroleum ether was added. The yellow precipitate was filtered and dissolved in water. The crude β-diketone precipitated after acidification and was used in the ring closure without further purification.

Crude diketone **22** was suspended in 20 mL ethanol, 1 mL concentrated HCl was added and the reaction mixture was heated for 3 h. The precipitate was filtered and recrystallized from ethanol to yield the pure flavones **23**. The esters were hydrolysed to the corresponding acids by refluxing the esters in 5 mL acetic acid with 0.6 mL concentrated HCl for 2 h. After cooling the precipitate was filtered and recrystallized from DMF.

Method C. A mixture of 0.65 g (1.7 mmol) 7-hydroxyflavone, 1.8 mmol ethyl α-chloroacetate or ethyl 3-bromomethylbenzoate, 0.45 g of NaI (3.0 mmol) and 0.32 g (2.39 mmol) of K_2CO_3 in 30 mL acetone was refluxed for 48 h. Filtration, evaporation of the solvent and crystallization from ethanol yielded the pure esters which were dissolved in 5 mL 2 N NaOH and 5 mL ethanol. After refluxing for 15 min the reaction mixture was acidified with concentrated HCl, the precipitates were filtered. Recrystallization from ethanol and ethyl acetate yielded **18** and **21** as white solids.

Method D. 7-Hydroxyflavone (1.0 g, 3.53 mmol), 4-bromobutyronitrile (0.47 g, 3.53 mmol) and K_2CO_3 (0.64 g, 4.64 mmol) in 15 mL DMF were stirred at 110 °C overnight. After addition of 40 mL water to the reaction mixture, the water layer was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with water (40 mL) and brine (40 mL), dried over Na_2SO_4 and evaporated. Yield: 63%; mp 105.1 °C; ^{1}H-NMR ($CDCl_3$): δ 2.17 (m, 2H), 2.60 (t, 2H, ^3J = 7.0 Hz), 4.15 (t, 2H, ^3J = 5.7 Hz), 6.70 (d, 1H, ^4J = 2.2 Hz), 6.92 (m, 2H), 7.47 (m, 3H), 7.84 (m, 2H), 8.07 (dd, 1H, ^3J = 9.4 Hz, ^4J = 2.4 Hz). ^{13}C-NMR ($CDCl_3$): δ 14.00 (t), 24.95 (t), 65.78 (t), 100.90 (d), 107.20 (d), 114.35 (d), 117.87 (s), 118.77 (s), 125.94 (d), 126.92 (d), 128.83 (d), 131.34 (d), 131.42 (s), 157.64 (s), 162.63 (s), 162.96 (s), 177.61 (s). HRMS *m/e* (M^+) Calcd for $C_{19}H_{15}NO_3$ 305.1052. Found 305.1058 ± 0.0005. A mixture of 0.4 g (1.3 mmol) 7-[(3-cyano)propoxy]flavone, 0.21 g (3.3 mmol) NaN_3 and 0.18 g (3.3 mmol) NH_4Cl in 5 mL DMF was stirred at 110 °C for 2 days. The reaction mixture was acidified with 1 N HCl and the DMF was evaporated under vacuum. After addition of water the solid was filtered and recrystallized from ethanol to give 0.29 g (0.83 mmol) of **20** as a white solid.

Method E. Alkylation analogous to *Method D* using ethyl 5-bromovalerate. Crystallization from ethanol. Yield 49%; mp 95.7 °C; ^{1}H-NMR ($CDCl_3$): δ 1.18 (t, 3H, ^3J = 7.1 Hz), 1.77 (m, 4H), 2.33 (t, 2H, ^3J = 6.8 Hz), 4.00 (m, 2H), 4.06 (q, 2H, ^3J = 7.1 Hz), 6.66 (s, 1H), 6.87 (m, 2H), 7.43 (m, 3H), 7.79 (m, 2H), 8.02 (d, 1H, ^3J = 9.2 Hz). ^{13}C-NMR ($CDCl_3$): δ 14.08 (q), 21.36 (t), 28.21 (t), 33.65 (t), 60.21 (t), 67.95 (t), 100.65 (d), 107.27 (d), 114.57 (d), 117.53 (s), 125.94 (d), 126.77. (d), 128.81 (d), 131.22 (d), 131.63 (s), 157.76 (s), 162.76 (s), 163.34 (s), 173.13 (s), 177.66 (s). HRMS *m/e* (M^+) Calcd for $C_{22}H_{22}O_5$ 366.1467. Found 366.1470 ± 0.0005.

The ester was hydrolysed in a mixture of 2 mL methanol, 2 mL THF and 2 mL of 5% LiOH in water. After stirring overnight the reaction mixture was acidified, filtered and the product was recrystallized from ethanol, yielding **19**.

General procedure for flavanone synthesis

The chalcone (1–2 g) was dissolved in 15 mL ethanol and 1 mL 1% KOH/ethanol was added. The reaction mixture was refluxed for 6 h and monitored by TLC (dichloromethane or petroleum ether/ethyl acetate 10:1). The reaction was stopped by neutralization with 1 N HCl and after removal of the solvent the chalcone/flavanone mixtures were separated either by column chromatography with silica gel and dichloromethane (the esters), or by crystallization (**29**).

*Reduction of **28** with $NaBH_4$*

To a solution of 300 mg (1.0 mmol) **28** in 20 mL isopropanol at 40 °C was added 0.11 g (2.9 mmol) $NaBH_4$. After 30 min the starting material had disappeared (TLC, dichloromethane) and the reaction was quenched with a few drops of glacial acetic acid. The solvent was removed, water was added (20 mL) and the product was extracted with ethyl acetate (3 x 30 mL). The crude product was purified by column chromatography (dichloromethane/ether 1:1) and crystallized from ether/petroleum ether 40:60. **35** (0.15 g, 0.5 mmol) was obtained as off-white crystals.

*Synthesis of **36***

To a solution of 140 mg (0.47 mmol) **35** in 1 mL THF and 1 mL methanol, was added 1 mL of 5% LiOH in water. The reaction mixture was stirred over night and acidified with 1 N HCl. After addition of 20 mL water the product was extracted with ethyl acetate (3 x 30 mL), the combined organic layers were washed with brine (40 mL) and dried over Na_2SO_4. After removal of the solvent the crude product was washed with chloroform to remove traces of ester, 90 mg (0.33 mmol) of **36** was obtained as a white solid.

*Synthesis of **37***

To a solution of 0.15 g (0.5 mmol) **28** in 10 mL trifluoroacetic acid 0.2 g (5 mmol) of $NaBH_4$ was added over 5 h in small portions, the reaction mixture was stirred overnight. After addition of 30 mL water the suspension was made alkaline with 1 N NaOH, the product was extracted with ether (3 x 30 mL). The combined ether layers were washed with brine (40 mL) and dried over Na_2SO_4, the solvent was removed under reduced pressure. Recrystallization from methanol gave 0.10 g (0.35 mmol) **37**.

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Table IV. Physical data of flavones **13–21**.

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS (calc)*	*^{1}H-NMR*[c]	*^{13}C-NMR*[c]
13	27	>300 (lit 303–304 [13]) (EtOH)	266.0573 ± 0.0005 (266.0579)	(DMSO): δ 7.12 (s, 1H, H3), 7.56–7.65 (m, 3H, H3', H4', H5'), 7.89 (d, 1H, ^3J = 8.8 Hz, H8), 8.11–8.15 (m, 2H, H2', H6'), 8.28–8.33 (m, 1H, H7), 8.58 (m, 1H, H5), 13.35 (br s, 1H, CO_2H)	(DMSO): δ 106.93 (d), 118.97 (d), 122.74 (s), 126.19 (d), 126.45 (d), 127.52 (s), 128.88 (d), 130.51 (s), 131.78 (d), 134.11 (d),157.76 (s), 162.59 (s), 165.84 (s), 176.48 (s)
14	49	272.0[b] (EtOH)	280.0730 ± 0.0005 (280.0735)	(DMSO): δ 2.39 (s, 3H, $PhCH_3$), 7.11 (s, 1H, H3), 7.38 (d, 2H, ^3J = 8.2 Hz, H3', H5'), 7.56 (t, 1H, ^3J = 7.7 Hz, H6), 8.10 (d, 2H, ^3J = 8.2 Hz, H2', H6'), 8.22–8.28 (m, 2H, H5, H7)	(DMSO): δ 20.85 (q), 105.67 (d), 121.50 (s), 123.93 (s), 124.60 (d), 126.27 (d), 127.90 (s), 128.97 (d), 129.46 (d), 135.90 (d), 142.10 (s), 153.54 (s), 162.51 (s), 165.02 (s), 176.31 (s)
15	45	>300 (EtOH/DMF)	357.9837 ± 0.0005 (357.9841)	(DMSO): δ 2.38 (s, 3H, $PhCH_3$), 7.14 (s, 1H, H3), 7.37 (d, 2H, ^3J = 8.1 Hz, H3', H5'), 8.70 (d, 2H, ^3J = 8.1 Hz, H2', H6'), 8.27 (m, 1H, H5), 8.30 (m, 1H, H7)	(DMSO): δ 20.85 (q), 105.66 (d), 116.66 (s), 123.88 (s), 125.59 (s), 126.29 (d), 127.58 (s), 129.46 (d), 130.75 (d), 137.75 (d), 142.31 (s), 162.74 (s), 163.65 (s), 175.05 (s)
16	68	>300 (DMF)	317.0683 ± 0.0005 (317.0688)	(400 MHz, DMSO, 328 K): δ 7.46 (s, 1H, H3), 7.72–7.76 (m, 1H, H6-quinoline), 7.87 (m, 1H, H7-quinoline), 7.96 (d, 1H, ^3J = 8.7 Hz, H8), 8.10 (d, 1H, ^3J = 8.0 Hz, H5-quinoline), 8.17 (d, 1H, ^3J = 8.4 Hz, H8-quinoline), 8.35–8.38 (m, 2H, H7, H3-quinoline), 8.65–8.67 (m, 2H, H4-quinoline, H5)	(100 MHz, DMSO, 328K): δ 108.35 (d), 117.89 (d), 119.12 (d), 126.44 (d), 127.74 (d), 128.02 (s), 128.06 (d), 128.31 (s), 129.22 (d), 130.50 (d), 134.28 (d), 137.71 (d), 146.98 (s), 146.25 (s), 157.80 (s), 161.28 (s), 161.36 (s), 165.74 (s)
17	25	>300 (DMF)	394.9790 ± 0.0005 (394.9793)	(DMSO): δ 7.45 (s, 1H, H3), 7.73–7.76 (m, H, H6-quinoline), 7.84–7.88 (m, 1H, H7-quinoline), 8.66–8.10 (m, 2H, H5,8-quinoline), 8.30 (d, 1H, ^4J = 2.6 Hz, H5 or H7), 8.36 (d, 1H, ^4J = 2.6 Hz, H5 or H7), 8.38 (d, 1H, ^3J = 8.6 Hz, H3-quinoline), 8.67 (d, 1H, ^3J = 8.6 Hz, H4-quinoline)	(DMSO): δ 107.33 (d), 117.15 (s), 123.92 (s), 126.10 (s), 127.88 (d), 128.26 (d), 128.39 (s), 129.21 (d), 130.67 (d), 131.00 (d), 137.86 (d), 128.22 (d), 146.85 (s), 148.02 (s), 152.62 (s), 161.28 (s), 163.48 (s), 175.10 (s)

Table IV. *Continued*

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS (calc)*	*^{1}H-NMR*[c]	*^{13}C-NMR*[c]
18	70	264.3–265.0 (EtOH/DMF)	296.0685 ± 0.0008 (296.0685)	(DMSO): δ 4.78 (s, 2H, OCH_2CO_2H), 6.95 (s, 1H, H3), 7.07 (d, 1H, ^3J = 8.8 Hz, H6), 7.31 (s, 1H, H8), 7.59 (m, 3H, H3', H4', H5'), 7.93 (d, 1H, ^3J = 8.8 Hz, H5), 8.06 (m, 2H, H2', H6'), 13.18 (br s, 1H, OCH_2CO_2H)	(DMSO): δ 64.65 (t), 101.60 (d), 106.52 (d), 114.57 (d), 117.23 (s), 125.95 (d), 125.96 (d), 128.84 (d), 130.87 (s), 131.43 (d), 157.01 (s), 161.94 (s), 162.07 (s), 169.27 (s), 176.14 (s)
19	43	128.4[b] (EtOH)	338.1153 ± 0.0005 (338.1154)	($CDCl_3$): δ 1.82–1.89 (m, 4H, $OCH_2(CH_2)_2$), 2.37–2.49 (m, 2H, CH_2CO_2H), 4.05–4.10 (m, 2H, OCH_2), 6.77 (s, 1H, H3), 6.92 (d, 1H, J = 1.1 Hz, H8), 6.92–6.96 (m, 1H, H6), 7.47–7.51 (m, 3H, H3', H4', H5'), 7.85–7.91 (m, 2H, H2', H6'), 8.09 (dd, 1H, ^3J = 9.3 Hz, ^4J = 2.8 Hz, H5)	($CDCl_3$): δ 21.28 (t), 28.17 (t), 33.46 (t), 68.02 (t), 100.63 (d), 107.11 (d), 114.66 (d), 117.40 (s), 125.92 (d), 126.63 (d), 128.79 (d), 131.24 (d), 131.50 (s), 157.75 (s), 162.82 (s), 163.41 (s), 175.39 (s), 177.70 (s)
20	40	213.5–215.0 (EtOH)	348.1221 ± 0.0005 (348.1223)	(DMSO): δ 2.22 (m, 2H, OCH_2CH_2), 3.08 (t, 2H, ^3J = 7.4 Hz, CH_2CN_4H), 3.20 (t, 2H, ^3J = 6.0 Hz, OCH_2), 6.94 (s, 1H, H3), 6.99 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.2 Hz, H6), 7.28 (d, 1H, ^3J = 2.0 Hz, H8), 7.57 (m, 3H, H3', H4', H5'), 7.91 (d, 1H, ^3J = 8.8 Hz, H5), 8.06 (m, 2H, H2', H6')	($CDCl_3$): δ 19.35 (t), 26.11 (t), 67.09 (t), 101.16 (d), 106.51 (d), 114.70 (d), 116.90 (s), 125.92 (d), 128.81 (d), 130.90 (s), 131.39 (d), 157.18 (s), 161.86 (s), 162.70 (s), 176.15 (s)
21	55	195.8–199.9 EtOH/DMF)	372.0995 ± 0.0005 (372.0998)	(DMSO): δ 5.36 (s, 2H, OCH_2Ph), 6.96 (s, 1H, H3), 7.15 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.3 Hz, H6), 7.43 (d, 1H, ^4J = 2.3 Hz, H8), 7.51–7.58 (m, 4H, H3', H4', H5', H–aromatic), 7.73 (d, 1H, ^3J = 7.7 Hz, H-aromatic), 7.92 (d, 1H, 3J = 7.6 Hz, H-aromatic), 7.95 (d, 1H, ^3J = 8.8 Hz, H8), 8.04–8.09 (m, 3H, H2', H6', H-aromatic)	(DMSO): δ 69.04 (t), 101.56 (d), 106.41 (d), 114.67 (d), 116.97 (s), 125.76 (d), 125.88 (d), 128.09 (d), 128.50 (d), 128.65 (d), 128.66 (d), 130.68 (s), 130.73 (s), 131.23 (d), 131.72 (d), 136.31 (s), 156.96 (s), 161.76 (s), 162.31 (s), 166.68 (s), 175.98 (s)

[a]Overall yields. [b]Melting point measured on a Mettler FP–51 apparatus. [c]Spectra recorded on 200 MHz at room temperature, unless stated otherwise.

Table V. Physical data of chalcones **2–12**.

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS m/e (M^+)*	*^{1}H-NMR*	*^{13}C-NMR*
2	67	200.6-203.6 (EtOH/THF)	268.0732 ± 0.0005 (268.0735)	(DMSO): δ 7.09 (d, 1H, ^3J = 8.6 Hz, H3'), 7.46–7.49 (m, 3H, H3, H4, H5), 7.79 (d, 1H, ^3J = 15.6 Hz, H_α), 7.85–7.90 (m, 2H, H2, H6), 7.94 (d, 1H, ^3J = 15.6 Hz, H_β), 8.06 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.0 Hz, H4), 8.53 (d, 1H, ^4J = 2.0 Hz, H6'), 12.52 (br s, 1H, OH), 12.87 (br s, 1H, OH)	(DMSO): δ 117.61 (d), 121.62 (s), 121.85 (s), 122.78 (d), 128.77 (d), 128.90 (d), 130.75 (d), 132.18 (d), 134.16 (s), 135.86 (d), 144.48 (d), 163.62 (s), 166.30 (s), 192.52 (s)
3	70	179.6–180.0 (EtOH)	249.0791 ± 0.0007 (249.0790)	(DMSO): δ 7.17 (d, 1H, ^3J = 8.7 Hz, H3'), 7.47–7.50 (m, 3H, H3, H4, H5), 7.82 (d, 1H, ^3J = 15.6 Hz, H_α), 7.89–7.94 (m, 3H, H2, H6, H4'), 8.00 (d, 1H, ^3J = 15.6 Hz, H_β), 8.68 (d, 1H, ^4J = 2.0 Hz, H6'), 12.87 (s, 1H, ArOH)	(DMSO): δ 101.59 (s), 118.37 (s), 118.86 (d), 121.94 (d), 122.19 (s), 128.74 (d), 129.08 (d), 131.00 (d), 134.07 (d), 135.57 (d), 138.17 (d), 145.43 (d), 163.84 (s), 192.02 (s)
4	78	237.7–238.4 (EtOH)	282.0890 ± 0.0005 (282.0892)	(DMSO): δ 2.30 (s, 3H, $PhCH_3$), 6.78 (t, 1H, ^3J = 7.6 Hz, H5'), 7.22 (d, 2H, ^3J = 7.8 Hz, H3, H5), 7.56 (d, 1H, ^3J = 15.8 Hz, H_α), 7.58 (d, 2H, ^3J = 7.8 Hz, H5, H9), 7.73 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.8 Hz, H6'), 7.83 (d, 1H, ^3J = 15.8 Hz, H_β), 7.98 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.8 Hz, H4')	(DMSO): δ 20.79 (q), 115.95 (d), 119.07 (s), 125.66 (d), 128.15 (d), 129.37 (d), 131.94 (s), 133.75 (d), 134.45 (d), 139.99 (s), 141.16 (d), 163.65 (s), 171.16 (s), 190.52 (s)
5	58	200–207 (EtOH)	269.0691± 0.0009 (269.0688)	(DMSO): δ 7.09 (d, 1H, ^3J = 8.7 Hz, H3'), 7.44 (m, 1H, H5–py), 7.73 (d, 1H, ^3J = 15.4 Hz, H_α), 7.85–7.89 (m, 2H, H3, 4–py), 8.03 (d, 1H, ^3J = 8.7 Hz, H3'), 8.15 (d, 1H, ^3J = 15.4 Hz, H_β), 8.39 (s, 1H, H6'), 8.68 (d, 1H, ^3J = 3.9 Hz, H6-py), 12.20 (s, 1H, ArOH), 12.92 (br s, 1H, ArCOOH)	(DMSO): δ 117.64 (δ), 121.63 (s), 121.86 (s), 124.77 (d), 125.44 (d), 125.70 (d), 132.01 (d), 135.90 (d), 136.99 (d), 142.70 (d), 149.85 (d), 152.09 (s), 163.46 (s), 166.20 (s), 192.18 (s)
6	53	120.3–121.6 (EtOH)	297.1002 ± 0.0007 (297.1001)	($CDCl_3$): δ 1.36 (t, 3H, ^3J = 7.1Hz, OCH_2CH_3), 4.35 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 7.00 (d, 1H, ^3J = 8.8 Hz, H3'), 7.29 (m, 1H, H5-py), 7.47 (d, 1H, ^3J = 7.5 Hz, H3-py), 7.73 (m, 1H, H4-py), 7.86 (d, 1H, ^3J = 15.0 Hz, H_α), 8.12 (d, 1H, ^3J = 8.8 Hz, H4'), 8.25 (d, 1H, J = 15.0 Hz, H_β), 8.70 (m, 2H, H6', H6-py), 13.19 (br s, 1H, ArOH)	($CDCl_3$): δ 14.13 (q), 60.81 (t), 118.30 (d), 119.14 (s), 121.16 (s), 123.08 (d), 124.74 (d), 125.70 (d), 132.21 (d), 136.77 (d), 136.98 (d), 144.25 (d), 150.02 (d), 152.14 (s), 165.14 (s), 166.73 (s), 193.63 (s)
7	87	216.7–219.5 (EtOH/THF)	318.0886 ± 0.0007 (318.0892)	(DMSO): δ 7.11 (d, 1H, ^3J = 8.7 Hz, H3'), 7.57–7.62 (m, 2H, H6,7-naphthyl), 7.91–8.13 (m, 7H, H4', H_α, H_β, H3, 4,5,8-naphthyl), 8.37 (s, 1H, H1-naphthyl), 8.58 (d, 1H, ^4J = 2.0 Hz, H6'), 12.58 (s, 1H, ArOH), 12.94 (br s, 1H, $ArCO_2H$)	(DMSO): δ 117.64 (d), 121.63 (s), 121.76 (s), 122.86 (d), 124.21 (d), 126.62 (d), 127.44 (d), 127.50 (d), 128.34 (d), 128.44 (d), 140.97 (d), 131.81 (s), 132.17 (d), 132.67 (s), 133.83 (s), 135.91 (d), 144.63 (d), 163.78 (s), 166.33 (s), 192.55 (s)

Table V. *Continued.*

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS m/e (M^+)*	*^{1}H-NMR*	*^{13}C-NMR*
8	37	124.6–126.8 (EtOH)	346.1208 ± 0.0007 (346.1205)	($CDCl_3$): δ 1.41 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 4.40 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 7.04 (d, 1H, ^3J = 8.8 Hz, H3'), 7.53 (m, 2H, H6,7–naphthyl), 7.80 (d, 1H, ^3J = 15.5 Hz, H_α), 7.84 (m, 4H, H3,4,5,8-naphthyl), 8.11 (d, 1H, ^3J = 15.5 Hz, H_β), 8.15 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.0 Hz, H4'), 8.70 (d, 1H, ^4J = 2.0 Hz, H6'), 13.37 (s, 1H, ArOH)	($CDCl_3$): δ 14.27 (q), 61.01 (t), 118.54 (d), 119.23 (d), 121.08 (d), 123.64 (d), 126.76 (d), 127.63 (d), 127.69 (d), 128.66 (d), 128.74 (d), 131.36 (d), 131.64 (s), 131.98 (d), 133.12 (s), 134.53 (s), 136.79 (d), 146.47 (d), 161.24 (s), 165.53 (s), 167.03 (s), 193.24 (s)
9	59	107.6–109.2 (EtOH)	346.1208 ± 0.0006 (346.1205)	($CDCl_3$ + a little DMSO): δ 1.08 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 4.06 (q, 2H, 3J = 7.1 Hz, OCH_2CH_3), 6.73 (d, 1H, ^3J = 8.8 Hz, H3'), 7.23–7.33 (m, 3H, H3,6,7-naphthyl), 7.50 (d, 1H, ^3J = 15.2 Hz, H_α), 7.58–7.71 (m, 3H, H4, H5, H8-naphthyl), 7.83 (d, 1H, ^3J = 8.8 Hz, H2–naphthyl), 7.94 (d, 1H, ^3J = 8.8 Hz, H4'), 8.37 (s, 1H, H6'), 8.48 (d, 1H, ^3J = 15.2 Hz, H_β), 12.94 (br s, 1H, ArOH)	($CDCl_3$ + a little DMSO): δ 14.10 (q), 60.78 (t), 118.32 (d), 119.07 (s), 121.02 (s), 121.64 (d), 122.83 (d), 125.21 (d), 125.41 (d), 126.14 (d), 126.95 (d), 128.59 (d), 131.16 (s), 131.30 (d), 131.39 (s), 131.86 (d), 133.37 (s), 136.70 (d), 142.78 (d), 165.13 (s), 166.69 (s), 192.97 (s)
10	66	140.0–140.7 (EtOH)	330.0658 ± 0.0006 (330.0659)	($CDCl_3$): δ 1.41 (q, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 4.39 (q , 2H, ^3J = 7.1 Hz, OCH_2CH_3), 7.04 (d, 1H, ^3J = 8.8 Hz, H3'), 7.42 (d, 2H, ^3J = 8.5 Hz, H3, H5), 7.63 (d, 2H, ^3J = 8.5 Hz, H2, H6), 7.68 (d, 1H, ^3J = 15.4 Hz, H_α), 7.91 (d, 1H, ^3J = 15.4 Hz, H_β), 8.16 (dd, 1H, ^3J = 8.8 Hz , ^4J = 2.0 Hz, H4'), 8.64 (d, 1H, ^4J = 2.0 Hz, H6'), 13.23 (s, 1H, ArOH)	($CDCl_3$): δ 14.24 (q), 61.05 (t), 118.60 (d), 119.17 (s), 119.72 (d), 121.15 (s), 129.25 (d) 129.90 (d), 131.97 (d), 132.62 (s), 136.95 (d), 137.10 (s), 144.87 (d), 165.49 (s), 166.98 (s), 193.14 (s)
11	77	126.7–128.7 (EtOH)	326.1159 ± 0.0005 (326.1154)	($CDCl_3$): δ 1.41 (q , 3H, ^3J = 7.2 Hz, OCH_2CH_3), 3.87 (s, 3H, OCH_3), 4.39 (q, 2H, ^3J = 7.2 Hz, OCH_2CH_3), 6.96 (d, 2H, ^3J = 8.8 Hz, H3, H5), 7.02 (d, 1H, ^3J = 8.7 Hz, H3'), 7.59 (d, 1H, ^3J = 15.4 Hz, H_α), 7.66 (d, 2H, ^3J = 8.8 Hz, H2, H6), 7.95 (d, 1H, ^3J = 15.4 Hz, H_β), 8.13 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H4'), 8.65 (d, 1H, ^4J = 2.1 Hz, H6'), 13.46 (s, 1H, ArOH)	$CDCl_3$): δ 14.24 (q), 55.27 (q), 60.91 (t), 114.36 (d), 116.61 (d), 118.43 (d), 119.29 (s), 120.93 (s), 126.88 (s), 130.71 (d), 131.81 (d), 136.54 (d), 146.24 (d), 162.12 (s), 165.51 (s), 166.97 (s), 193.16 (s)
12	5	193.9–195.5 (EtOH)	319.0842 ± 0.0007 (319.0845)	(DMSO): δ 7.13 (d, 1H, ^3J = 8.7 Hz, H3'), 7.65–7.70 (m, 1H, H6-quinoline), 7.81–7.89 (m, 2H, H_α, H7-quinoline), 8.08–8.19 (m, 4H, H4', H3-quinoline, H5-quinoline, H8-quinoline), 8.32 (d, 1H, ^3J = 17 Hz, H_β), 8.49–8.55 (m, 2H, H4-quinoline, H6')	(DMSO/$CDCl_3$): δ 117.66 (d), 119.87 (s), 121.22 (d), 121.59 (s), 125.13 (d), 127.04 (d), 127.27 (s), 127.64 (s), 129.06 (d), 129.61 (d), 132.11 (d), 135.97 (d), 136.51 (d), 144.05 (d), 147.56 (s), 152.48 (s), 165.03 (s), 166.20 (s), 192.85 (s)

[a]Unoptimized yields.

Table VI. Physical data of **28–37**.

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS m/e (M^+)*	*^{1}H-NMR*	*^{13}C-NMR*
28	48	102.0–103.9 (EtOH)	296.1054 ± 0.0005 (296.1049)	($CDCl_3$): δ 1.38 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 2.93 (dd, 1H, ^2J = 16.9 Hz, ^3J = 3.4 Hz, H3-eq), 3.11 (dd, 1H, ^2J = 16.9 Hz, ^3J = 12.7 Hz, H3-ax), 4.35 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.52 (dd, 1H, ^3J = 12.6 Hz, ^3J = 3.4 Hz, H2), 7.08 (d, 1H, ^3J = 8.7 Hz, ,H8), 7.40–7.47 (m, 5H, Ph), 8.17 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H7), 8.61 (d, 1H, ^4J = 2.2 Hz, H5)	($CDCl_3$): δ 14.19 (q), 44.15 (t), 60.99 (t), 79.75 (d), 118.26 (d), 120.21 (s), 124.02 (s), 126.01 (d), 128.77 (d), 128.86 (d), 129.18 (d), 136.79 (d), 137.90 (s), 164.32 (s), 165.34 (s), 190.87 (s)
29	36	201.5–202.2 (EtOH/THF)	269.0686 ± 0.0006 (269.0688)	(DMSO): δ 3.10 (dd, 1H, ^2J = 16.8 Hz, ^3J = 3.8 Hz, H3-eq), 3.38 (dd, 1H, ^2J = 16.8 Hz, ^3J = 10.8 Hz, H3-ax), 5.97 (dd, 1H, ^3J = 10.8 Hz, ^3J = 3.8 Hz, H2), 7.21 (d, 1H, ^3J = 8.6 Hz, H8), 7.52 (m, 1H, H5-py), 7.75 (d, 1H, ^3J = 7.7 Hz, H3-py), 8.06 (m, 2H, H7, H4-py), 8.32 (s, 1H, H5), 8.63 (d, 1H, ^3J = 4.3 Hz, H6-py)	(DMSO): δ 40.74 (t), 78.09 (d), 118.33 (d), 120.19 (s), 122.35 (d), 123.94 (s), 124.37 (d), 127.70 (d), 136.30 (d), 139.28 (d), 147.38 (d), 155.11 (s), 162.89 (s), 165.93 (s), 189.97 (s)
30	71	107.2–108.4 (EtOH)	297.1003 ± 0.0005 (297.1001)	($CDCl_3$): δ 1.37 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 3.12 (dd, 1H, ^2J = 17.1 Hz, ^3J = 4.7 Hz, H3-eq), 3.27 (dd, 1H, ^2J = 17.1 Hz, ^3J = 10.7 Hz, H3-ax), 4.35 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.65 (dd, 1H, ^3J = 10.7 Hz, ^3J = 4.7 Hz, H2), 7.11 (d, 1H, ^3J = 8.7 Hz, H8), 7.28 (m, 1H, H5-py), 7.56 (d, 1H, ^3J = 7.7 Hz, H3-py), 7.75 (dt, 1H, ^3J = 7.7 Hz, ^4J = 1.7 Hz, H4-py), 8.17 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H7), 8.60 (m, 2H, H5, H6-py)	($CDCl_3$): δ 14.18 (q), 42.18 (t), 60.98 (t), 79.79 (d), 118.20 (d), 120.51 (s), 120.95 (d), 123.48 (d), 124.15 (s), 129.14 (d), 136.73 (d), 137.12 (d), 149.26 (d), 156.67 (s), 163.71 (s), 165.33 (s), 190.52 (s)
31	53	118.4–124.3 (EtOH)	346.1206 ± 0.0006 (346.1205)	($CDCl_3$): δ 1.39 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 3.02 (dd, 1H, ^2J = 16.9 Hz, ^3J = 3.3 Hz, H3-eq), 3.22 (dd, 1H, ^2J = 16.9 Hz, ^3J = 12.6 Hz, H3-ax), 3.37 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.70 (dd, 1H, ^3J = 12.6 Hz, ^3J = 3.3 Hz, H2), 7.13 (d, 1H, ^3J = 8.7 Hz, H8), 7.50–7.60 (m, 3H, H5,6,7-naphthyl), 7.84–7.94 (m, 4H, H1,3,4,8-naphthyl), 8.19 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H7), 8.63 (d, 1H, ^4J = 2.2 Hz, H5)	($CDCl_3$): δ 14.20 (q), 44.16 (t), 61.01 (t), 79.87 (d), 118.31 (d), 120.28 (s), 123.36 (d), 124.10 (s), 125.38 (d), 126.52 (d), 126.59 (d), 127.63 (d), 128.00 (d), 128.77 (d), 129.24 (d), 132.94 (s), 133.27 (s), 135.19 (s), 136.86 (d), 164.33 (s),165.59 (s), 190.83 (s)
32	36	112.8–113.8 (EtOH)	346.1208 ± 0.0006 (346.1205)	($CDCl_3$): δ 1.40 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 3.13 (dd, 1H, ^2J = 17.1 Hz, ^3J = 3.6 Hz, H3-eq), 3.29 (dd, 1H, ^2J = 17.1 Hz, ^3J = 12.3 Hz, H3-ax), 4.38 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 6.27 (dd, 1H, ^3J = 12.3 Hz, ^3J = 3.6 Hz, H2), 7.12 (d, 1H, ^3J = 8.7 Hz, H8), 7.49–7.57 (m, 3H, H3,6,7-naphthyl), 7.75 (d, 1H, ^3J = 6.9 Hz, H8-naphthyl), 7.88–7.94 (m, 2H, H4,5-naphthyl), 7.99–8.04 (m, 1H, H2-naphthyl), 8.19 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H7), 8.67 (d, 1H, ^4J = 2.2 Hz, H5)	($CDCl_3$): δ 14.22 (q), 43.47 (t), 61.02 (t), 76.97 (d), 118.34 (d), 120.36 (s), 122.50 (d), 123.76 (d), 124.15 (s), 125.19 (d), 125.92 (d), 126.69 (d), 129.47 (d), 129.92 (s), 133.33 (s), 133.69 (s), 136.81 (d), 164.50 (s), 165.35 (s), 191.13 (s)

Table VI. *Continued.*

Compound	*Yield (%)*[a]	*Mp (°C) (crystallization solvent)*	*HRMS m/e (M^+)*	*^{1}H-NMR*	*^{13}C-NMR*
33	36	140.2–142.1 (EtOH)	364.0266 ± 0.0010 (364.0269)	($CDCl_3$): δ 1.33 (t , 3H, ^3J = 7.1 Hz, OCH_2CH_3), 2.85 (dd, 1H, ^2J = 16.9 Hz, ^3J = 4.3 Hz, H3-eq), 2.99 (dd, 1H, ^2J = 16.9 Hz, ^3J = 11.9 Hz, H3-ax), 4.31 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.43 (dd, 1H, ^3J = 11.8 Hz, ^3J = 4.3 Hz, H2), 7.04 (d, 1H, ^3J = 8.7 Hz, H8), 7.23 (dd, 1H, ^3J = 8.3 Hz, ^4J = 2.0 Hz, H6'), 7.45 (d, 1H, ^3J = 8.3 Hz, H5'), 7.54 (d, 1H, ^4J = 2.0 Hz, H2'), 8.14 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.2 Hz, H7) 8.50 (d, 1H, ^4J = 2.2 Hz, H5)	($CDCl_3$): δ 14.18 (q), 44.02 (t), 61.08 (t), 78.27 (d), 118.21 (d), 120.14 (s), 124.44 (s), 125.14 (d), 128.03 (d), 129.20 (d), 130.78 (d), 132.92 (s), 133.06 (s), 136.97 (d), 138.12 (s), 163.77 (s), 165.20 (s), 189.95 (s)
34	25	111.6–112.4 (EtOH)	326.1150 ± 0.0009 (326.1154)	($CDCl_3$): δ 1.38 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 2.90 (dd, 1H, ^2J = 16.9 Hz, ^3J = 3.2 Hz, H3-eq), 3.13 (dd, 1H, ^2J = 16.9 Hz, ^3J = 12.8 Hz, H3-ax), 3.82 (s, 3H, OCH_3), 4.35 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.47 (dd, 1H, ^3J = 12.9 Hz, ^3J = 3.1 Hz, H2), 6.90 (d, 2H, ^3J = 8.8 Hz, H3', H5'), 7.06 (d, 1H, ^3J = 8.8 Hz, H8), 7.39 (d, 2H, ^3J = 8.8 Hz, H2', H6'), 8.15 (dd, 1H, ^3J = 8.8 Hz, ^4J = 2.2 Hz, H7), 8.60 (d, 1H, ^4J = 2.2 Hz, H5)	($CDCl_3$): δ 14.20 (q), 43.94 (t), 55.22 (q), 60.98 (t), 79.53 (d), 114.11 (d), 118.27 (d), 120.19 (s), 123.93 (s), 127.63 (d), 129.19 (d), 129.87 (s), 136.76 (d), 159.97 (s), 164.42 (s), 165,40 (s), 191.15 (s)
35	50	107.7–109.8 (ether/petroleum ether)	298.1209 ± 0.0006 (298.1205)	($CDCl_3$): δ 1.37 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 2.02 (d, 1H, ^3J = 8.2 Hz, CHO*H*), 2.06–2.23 (m, 1H, H3-eq), 2.54 (ddd, 1H, ^2J = 13.2 Hz, ^3J = 6.1 Hz, ^3J = 2.0 Hz, H3-ax), 4.34 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.05–5.18 (m, 1H, H4), 5.23 (dd, 1H, ^3J = 11.7 Hz, ^3J = 2.0 Hz, H2), 6.89 (d, 1H, ^3J = 8.6 Hz, H8), 7.37–7.44 (m, 5H, Ph), 7.88 (dd, 1H, ^3J = 8.6 Hz, ^4J = 2.2 Hz, H7), 8.23 (d, 1H, ^4J = 2.2 Hz, H8)	($CDCl_3$): δ 14.22 (q), 39.22 (t), 60.65 (t), 65.14 (d), 77.33 (d), 116.52 (d), 122.87 (s), 125.62 (s), 125.94 (d), 128.29 (d), 128.57 (d), 129.08 (d), 130.59 (d), 139.71 (s), 158.19 (s), 166.40 (s)
36	70	180.7–185.6 (EtOH/THF)	270.0890 ± 0.0005 (270.0892)	(DMSO): δ 1.87–2.05 (m, 1H, H3-eq), 2.31–2.39 (m, 1H, H3-ax), 4.93–5.05 (m, 1H, H4), 5.36 (d, 1H, ^3J = 10.6 Hz, CHO*H*), 5.75 (d, 1H, ^3J = 6.6 Hz, H2), 6.86 (d, 1H, ^3J = 8.5 Hz, H8), 7.36–7.46 (m, 5H, Ph), 7.73 (dd, 1H, ^3J = 8.5 Hz, ^4J = 2.0 Hz, H7), 8.14 (d, 1H, ^4J = 2.0 Hz, H5), 12.60 (br s, 1H, ArCOO*H*)	(DMSO): δ 39.10 (t), 63.29 (d), 76.88 (d), 115.73 (d), 122.44 (s), 126.02 (d), 127.33 (s), 127.92 (d), 128.28 (d), 129.05 (d), 129.51 (d), 140.18 (s), 157.65 (s), 166.92 (s)
37	70	78.3–79.7 (MeOH)	282.1257 ± 0.0005 (282.1256)	($CDCl_3$): δ 1.36 (t, 3H, ^3J = 7.1 Hz, OCH_2CH_3), 2.00–2.31 (m, 2H, H2), 2.74–3.09 (m, 2H, H3), 4.33 (q, 2H, ^3J = 7.1 Hz, OCH_2CH_3), 5.06 (dd, 1H, ^3J = 9.7 Hz, ^3J = 2.8 Hz, H1), 6.90 (d, 1H, ^3J = 9.1 Hz, H8), 7.35 (m, 5H, Ph), 7.81 (m, 2H, H7, H8)	($CDCl_3$): δ 14.24 (q), 24.68 (t), 29.36 (t), 60.43 (t), 78.12 (d), 116.65 (d), 121.41 (s), 122.33 (s), 125.75 (d), 127.88 (d), 128.43 (d), 129.04 (d), 131.39 (d), 140.85 (s), 158.88 (s), 166.41 (s)

[a]Unoptimized yields.

References

1 Wurm G (1990) *Deutsche Apoth Zeit* 130, 2306–2312
2 Atassi G, Briet P, Berthelon JJ, Collonges F (1985) *Eur J Med Chem Chim Ther* 20, 393–402
3 Cutler SJ, El-Kabbani FM, Keane C et al (1993) *Eur J Med Chem* 28, 407–414
4 Setnikar I, Ravasi MT, Da Re P (1960) *J Pharmacol Exp Ther* 130, 356–363
5 Momose K, Ohhata H, Yamamoto T et al (1991) *Yakuri to Chiryo* 19, 793–808
6 Nardi D, Leonardi A, Pennini R, Tajana A, Cazzulani P, Testa R (1993) *Arzneim Forsch/Drug Res* 43, 28–34
7 Kagechika H, Kawachi E, Hashimoto Y, Shudo K (1989) *J Med Chem* 32, 834–840
8 Pfister JR, Wymann WE, Schuler ME, Roszkowski AP (1980) *J Med Chem* 23, 335–338
9 Pfister JR (1975) *Ger Offen* C 07 D 311.30
10 Wurm G, Geres U (1977) *Arch Pharm* 310, 119–128
11 Wurm G, Geres U (1978) *Arch Pharm* 311, 177–183
12 Wurm G, Geres U (1979) *Arzneim-Forsch/Drug Res* 29 (I), 15–18
13 Doria G, Romeo C, Giraldi P et al (1978) *Eur J Med Chem, Chim Ther* 13, 33–39
14 Cairns H, Fitzmaurice D, Hunter D et al (1972) *J Med Chem* 15, 583–589
15 Chanarin N, Johnston SL (1994) *Drugs* 47, 12–24
16 Larsen JS, Acosta EP (1993) *Ann Pharmacother* 27, 898–903
17 Gianaris PG, Golish JA (1993) *Drugs* 46, 1–6
18 Ellis JL, Undem BJ (1994) *Am J Respir Crit Care Med* 149, 118–122
19 Mayatepek E, Hoffmann GF (1995) *Pediatric Res* 37, 1–9
20 Musser JH, Kreft AF, Bender RHW et al (1989) *J Med Chem* 32, 1176–1183
21 Huang FC, Galemmo JRA, Poli GB et al (1991) *J Med Chem* 34, 1704–1707
22 Sekizaki H (1988) *Bull Chem Soc Jpn* 61, 1407–1409
23 Matsumura H, Tsuchiya T, Takeda T, Imafuku K (1983) *Bull Chem Soc Jpn* 56, 2037–2043
24 Makrandi JK (1989) *Chem Ind* 607
25 Hsu KK, Chang SF (1977) *Taiwan K'o Hsueh* 31, 130–135
26 Chan TH, Stossel D (1986) *J Org Chem* 51, 2423–2428
27 Ford RE, Knowles P, Lunt E et al (1986) *J Med Chem* 29, 538–549
28 Da Re P, Sianesi E, Mancine V (1966) *Chem Ber* 99, 1962–1965
29 Shah DN, Shah NM (1949) *J Ind Chem Soc* 26, 235–238
30 Tashiro M (1979) *Synthesis* 921–937
31 McOmie JFW, Saleh SA (1973) *Tetrahedron* 29, 4003–4005
32 Tashiro M, Fukata G, Mataka S, Oe K (1975) *Org Prep Proc Int* 7, 231–236
33 Wu ESC, Cole TE, Davidson TA et al (1989) *J Med Chem* 32, 183–192
34 Appleton RA, Bantick JR, Chamberlain TR, Hardern DN, Lee TB, Pratt AD (1977) *J Med Chem* 20, 371–379
35 Zhang MQ, Wada Y, Sato F, Timmerman H (1995) *J Med Chem* 38, 2472–2477
36 Sprecher VA, Beck A, Gerspacher M, Sallmann A, Anderson GP, Subramanian N, Niederhauser U, Bray MA (1993) *J Lipid Mediators* 6, 265–273
37 Marfat A, Chambers R, Cheng J et al (1995) *Bioorg Med Chem Lett* 5, 1377–1382
38 Labelle M, Belley M, Gareau Y et al (1995) *Bioorg Med Chem Lett* 5, 283–288
39 Musser JH, Kreft AF, Bender RHW et al (1990) *J Med Chem* 33, 240–245
40 Youssefyeh RD, Magnien E, Lee TDY et al (1990) *J Med Chem* 33, 1186–1194
41 Laughton JJ, Evans PJ, Moroney MA, Hoult JRS, Halliwell B (1991) *Biochem Pharm* 42, 1673–1681
42 Ballesteros JF, Sanz MJ, Ubeda A et al (1995) *J Med Chem* 38, 2794–2797