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Synthesis and pharmacological evaluation of new cysLT$_1$ receptor antagonists

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Summary — This paper describes the synthesis and pharmacological evaluation of three series of compounds **4a–b**, **13a–k** and **19**, structurally related to the known potent cysLT$_1$ receptor antagonists **RG-12553**, **ICI-204219** and **ONO-1078**, respectively. The common structural feature of these new series is the presence of a 4-quinolone nucleus acting as a template for substitution of the aromatic nucleus present in the prototype antagonists. We describe the evolution of these series leading to antagonists with potency at nanomolar concentrations in vitro.

leukotriene D$_4$ / antagonist / 4-quinolone / acylsulfonamide / molecular modelling

Introduction

Since the discovery in 1979 of the naturally-occurring peptidoleukotrienes (pLTs) [1–4], the antagonism of pLTs at their receptors has been the object of intense research [5, 6]. These agents are expected to be of value for the treatment of allergic asthma and other immediate hypersensitivity diseases [7, 8]. Indeed, over the past few years, extremely potent pLT antagonists have been developed [9, 10] and their effectiveness in the clinical treatment of asthma has been established [11–13]. Among others, the Zeneca indole series of compounds, exemplified by **ICI-204219** [14] and the chromone compounds **ONO-1078** [15] and **RG-12553** [16] (see fig 1) have been shown to be potent selective pLT antagonists with demonstrated clinical efficacy in the treatment of asthma symptoms [17–19].

This paper describes the synthesis and pharmacological evaluation in vitro of new compounds related to these antagonists. Compounds **A**, **B**, and **C** have a 4-quinolone nucleus as a template for substitution of the chromone, the indole or the central phenyl nucleus present in **RG-12553**, **ICI-204219** and **ONO-1078**, respectively.

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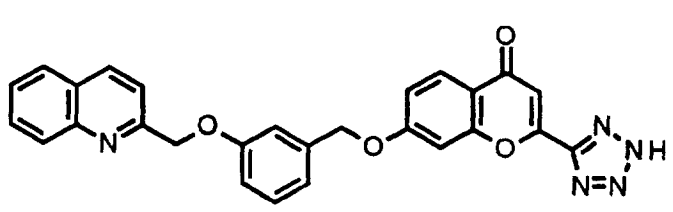
All structural modifications explored were based on both classical and computer-aided approaches. We describe the evolution of this series to antagonists with potency at nanomolar concentrations in vitro.

Chemistry

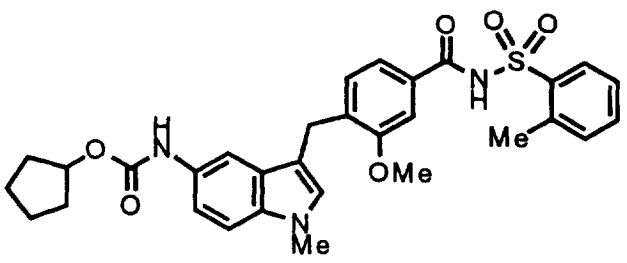
Three methods were used in preparing the 4-quinolones **2** shown in scheme 1.

The quinolones **2a–c** were obtained following the method described by Conrad and Limpach [20] (*Method A*, scheme 1). Condensation of *N*-methyl-3-benzyloxyaniline or 3-aminophenol acetate with dimethyl acetylenedicarboxylate (DMAD), with methanol as solvent and Triton B as base followed by acidic [21] (R^1 = Me) or thermal [22] (R^1 = H) cyclization of the dimethyl anilinobutendioate **1a** and **1b** yielded quinolones **2a–c**. In both sequences, deprotection of the phenol group took place. The acetate group was removed in the basic medium during the formation of **1b** and the benzyl protective group of **1a** was eliminated with the acidic medium of cyclization. Whilst the cyclization of **1a** gave a mixture of the regioisomers **2a** and **2b**, the cyclization of **1b** yielded only the quinolone **2c**. Compounds **2a** and **2b** were easily separated by column chromatography.

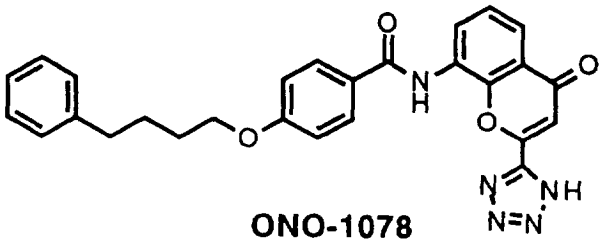
The target acids **4a** and **4b** were prepared (scheme 2) by condensation of phenols **2b** and **2c** in basic conditions with the mesyl derivative **3**. Compound **3** was obtained by reaction of the 3-hydroxymethylphenyl



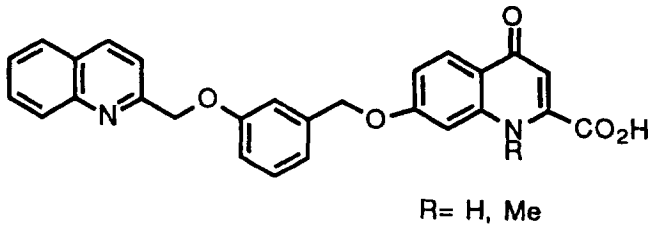
RG-12553



ICI-204219

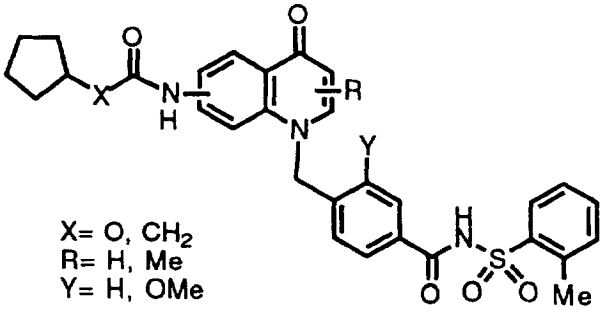


ONO-1078



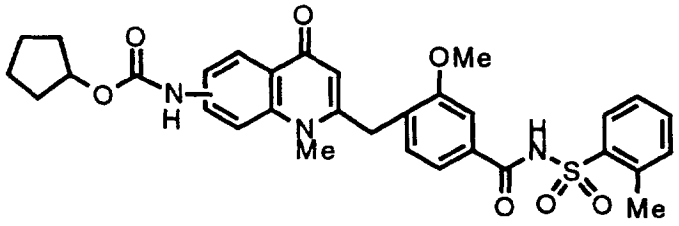
R= H, Me

A

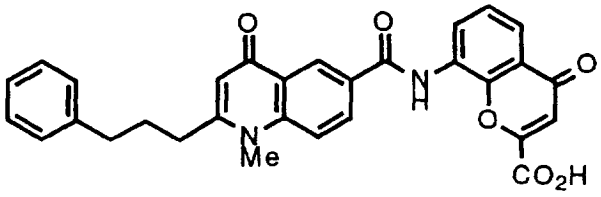


X= O, CH_2
R= H, Me
Y= H, OMe

B-1



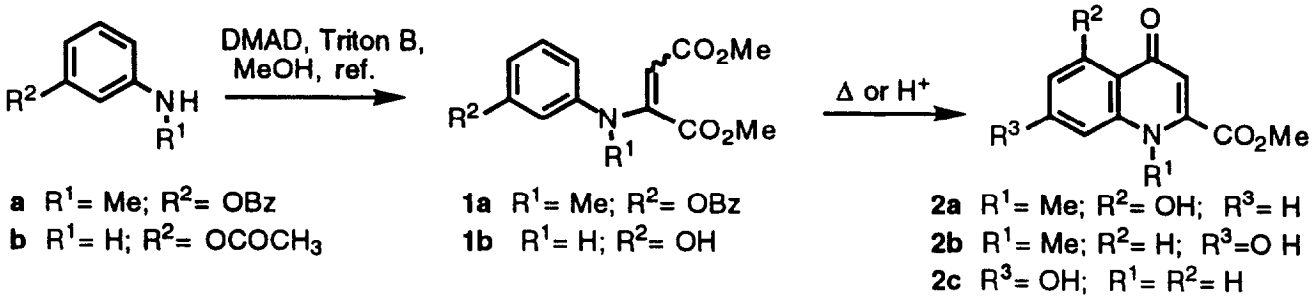
B-2



C

Fig 1. Studied compounds (**A**, **B**, **C**) related to compounds of demonstrated clinical efficacy in the treatment of asthma (**ICI-204219**, **ONO-1078**, **RG-12553**).

Method A

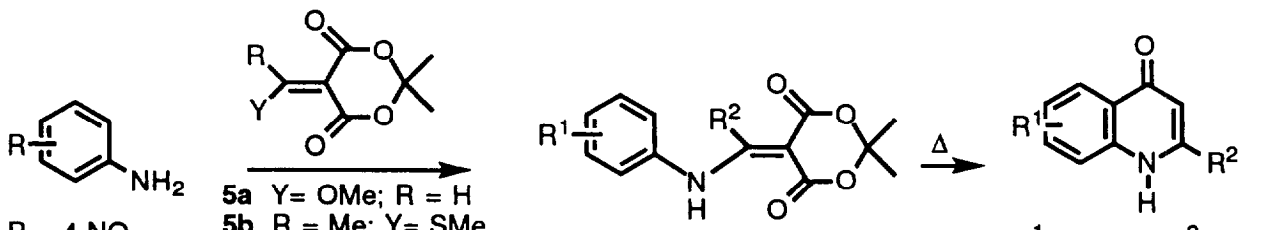


a R^1= Me; R^2= OBz
b R^1= H; R^2= $OCOCH_3$

1a R^1= Me; R^2= OBz
1b R^1= H; R^2= OH

2a R^1= Me; R^2= OH; R^3= H
2b R^1= Me; R^2= H; R^3=O H
2c R^3= OH; R^1= R^2= H

Method B



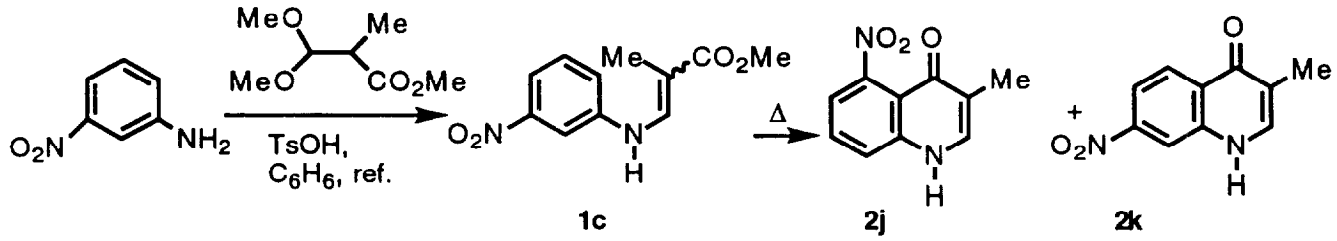
R = 4-NO_2
R = 3-NO_2
R = 4-CO_2Me

5a Y= OMe; R = H
5b R = Me; Y= SMe
5c R = $C_6H_5(CH_2)_3$; Y= SMe

6a R^1= 4-NO_2; R^2 = H
6b R^1= 3-NO_2; R^2 = H
6c R^1= 3-NO_2; R^2= Me
6d R^1= 6-CO_2Me; R^2= $C_6H_5(CH_2)_3$;

2d R^1= 6-NO_2; R^2= H
2e R^1= 5-NO_2; R^2= H
2f R^1= 7-NO_2; R^2= H
2g R^1= 5-NO_2; R^2= Me
2h R^1= 7-NO_2; R^2= Me
2i R^1= 6-CO_2Me; R^2= $C_6H_5(CH_2)_3$;

Method C



1c **2j** **2k**

Scheme 1. Methods A, B and C used in preparing the 4-quinolones **2**.

2-quinolylmethyl ether [23] with mesyl chloride in standard conditions. Both compounds **4a** and **4b** yielded similar low quantities.

Quinolones **2d–i** were prepared by condensation of the appropriate anilines with Meldrum's acid derivatives **5a–c**, followed by thermal cyclization of the resulting synthetic intermediates **6a–d** (*Method B*, scheme 1). Valderrama's method [24] was used to prepare Meldrum's acid derivative **5a** and for the further reaction of this compound with 4-nitroaniline or 3-nitroaniline to give **6a** and **6b**, respectively. Thermal cyclization of **6a** by heating in diphenyl ether solution afforded **2d**, and the same method of cyclization of **6b** gave two regioisomers, the quinolones **2e** and **2f**, the separation of which was not possible at this stage under standard chromatographic conditions. However, after *N*-alkylation they were resolved by column chromatography. The same method was used to prepare quinolones **2g** and **2h**: condensation of 3-nitroaniline with Meldrum's acid derivative **5b** [25, 26] (R = Me, Y= SMe) afforded **6c**, and thermal cyclization of **6c** gave a mixture of **2g** and **2h**. Finally, quinolone **2i**, possessing a phenylpropyl substituent in the 2-position, was prepared by condensation and thermal cyclization of methyl 4-aminobenzoate and **5c**. An extension of Huang's [25] procedure was used to obtain reasonable yields of **5c** and in the following reaction [26] to afford **6d**, thereby demonstrating the usefulness of this method for preparing synthetic precursors of 2-arylalkyl-4-quinolones and the substituted quinolone.

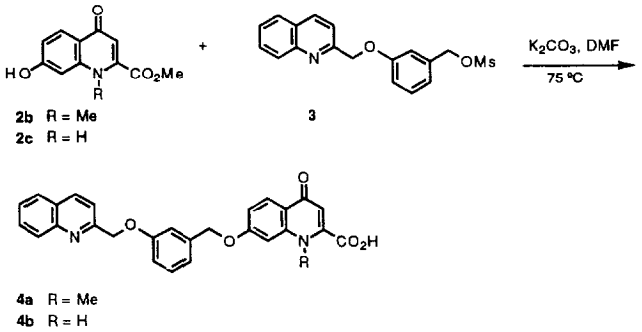
Quinolones **2j** and **2k** were obtained using a modified version of Conrad Limpach Knorr's synthesis [27] (*Method C*, scheme 1). Our modification involved the use of a protected β-formylester for the introduction of the three carbon atoms required for building the 4-quinolone system instead of a free formyl group. This was done to avoid secondary reactions. Thus, acid-catalysed condensation between 3-nitroaniline and methyl 2-methyl-3,3-dimethoxypropionate [28] yielded **1c** as a mixture of *Z* and *E* isomers. These were easily separated by column chromatography (see *Experimental protocols*). Isomers ***Z*-1c** and ***E*-1c** could be differentiated by the chemical shift (7.15 and 7.88 ppm, respectively) of the vinylic proton in the ^{1}H-NMR spectrum. Thermal cyclization of each isolated isomer or the ***Z,E*-1c** mixture yielded the same result, a mixture of regioisomers **2j** and **2k**. Again this mixture could only be separated after *N*-alkylation.

N-Methylation of quinolone **2d** with methyl iodide using KOH as a base in methanolic solution afforded the quinolone **2l**. The same procedure was used for the regioisomer mixture **2e** and **2f**, yielding a mixture of quinolones **2m** and **2n**, which were separated by column chromatography.

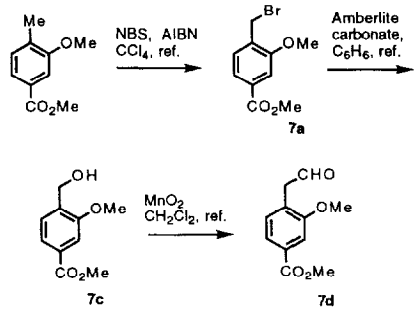
The key step in preparing compounds **9a** and **9b** from quinolones **2l** and **2n** respectively was the introduction of benzyl substituents in the 2-position of the heterocyclic ring (scheme 4). First, we used the method of *ortho*-lithiation of 4-quinolones [29] followed by the reaction of lithium derivatives of **2l** and **2n** with the benzyl bromide **7a**, but this procedure afforded the compounds **9a** and **9b** in very low yields. Alternatively, chemoselective condensation of 2-lithium derivatives of quinolones **2l** and **2n** with the aldehyde **7d** (scheme 3) afforded the alcohols **8a** and **8b**.

The reduction of **8a** and **8b** was afforded by treatment of their mesyl derivatives **8c** and **8d** with sodium borohydride in *i*-propanol, giving the benzyl derivatives **9a** and **9b** (scheme 4). The use of methanol as a solvent in the reduction yielded the methoxybenzyl derivative as a consequence of nucleophilic displacement of the mesyl-leaving group by the solvent.

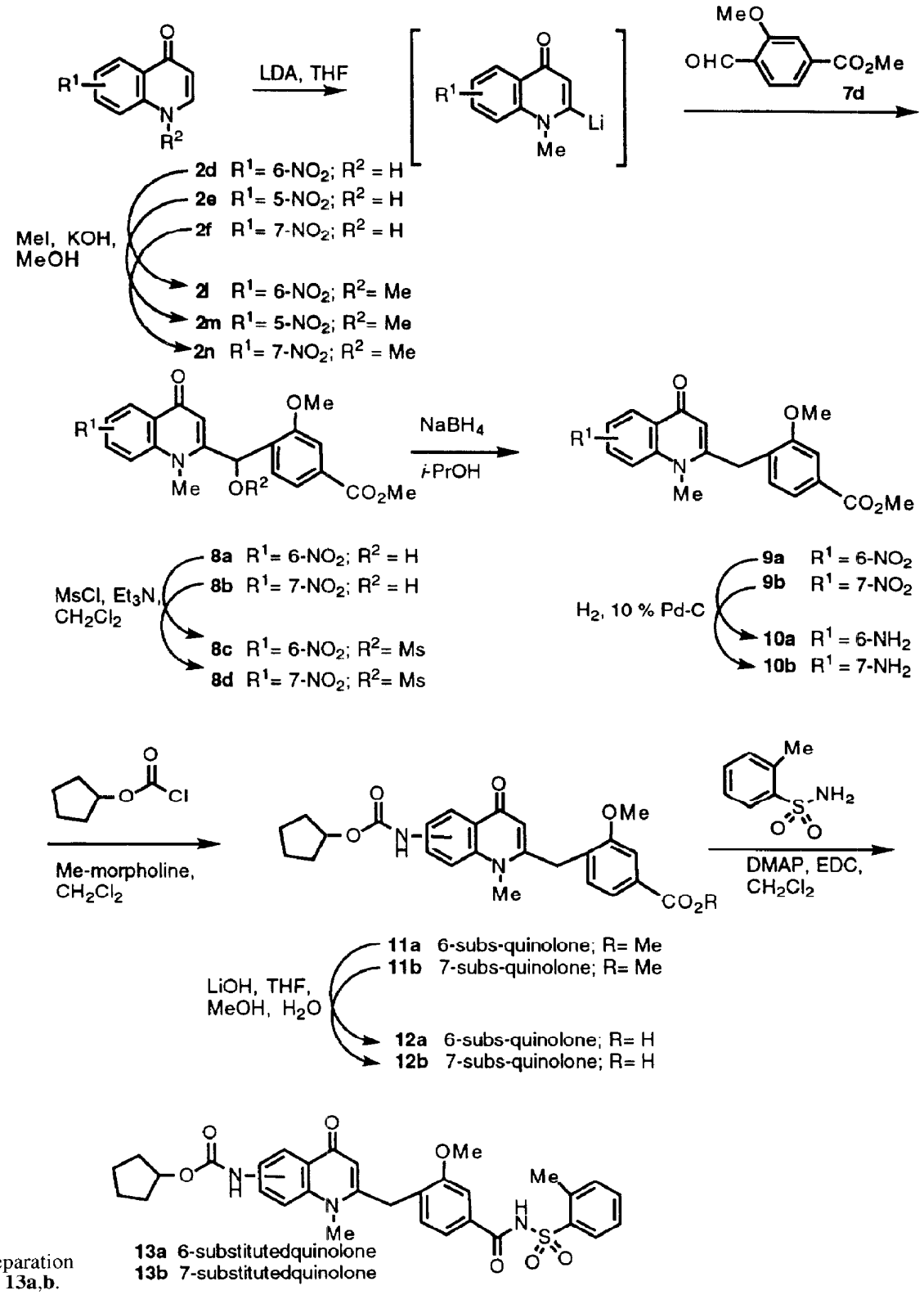
The quinolones **8e–o** with the benzyl substituents on the nitrogen were obtained by *N*-alkylation of quinolones **2d–h**, **2j**, and **2k** with the appropriate bromide **7a** or **7b** using NaH as a base in a solution of dry THF (scheme 5). Comparison of the ^{1}H-NMR



Scheme 2. Preparation of compounds **4a,b**.

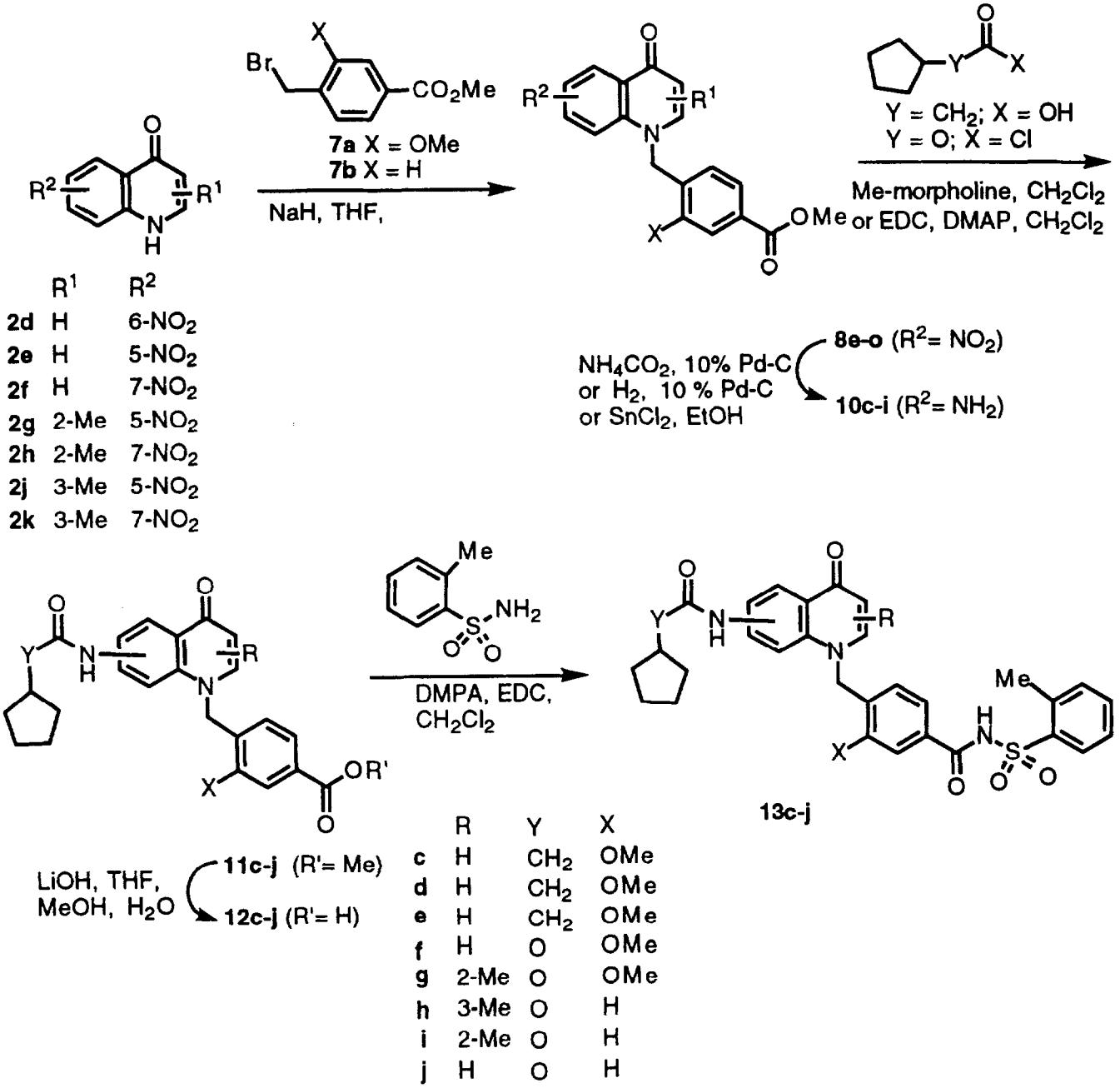


Scheme 3. Structure of compounds **7a,c,d**.



Scheme 4. Preparation of compounds **13a,b**.

spectrum of quinolones **8h** and **8i** with the analogues without the methyl group in position 2 of the heterocyclic ring, **8f** and **8g**, showed two main differences: the signal of H-3 was lowered 0.5–0.6 ppm, and H-8 was also deshielded between 0.5 and 0.8 ppm. The spectroscopic differences between the 2-methyl substituted 4-quinolones and those that were unsubstituted in the same position are maintained for the other derivatives of the synthetic sequence and are attributed to the steric hindrance between the 2-methyl and 2-methoxy groups, which seem to reduce the rotation of the benzylic substituents. This reduced rotation is also responsible for the loss of activity in compound **13g** (see later).



	R^1	R^2
2d	H	6-NO_2
2e	H	5-NO_2
2f	H	7-NO_2
2g	2-Me	5-NO_2
2h	2-Me	7-NO_2
2j	3-Me	5-NO_2
2k	3-Me	7-NO_2

	R	Y	X
c	H	CH_2	OMe
d	H	CH_2	OMe
e	H	CH_2	OMe
f	H	O	OMe
g	2-Me	O	OMe
h	3-Me	O	H
i	2-Me	O	H
j	H	O	H

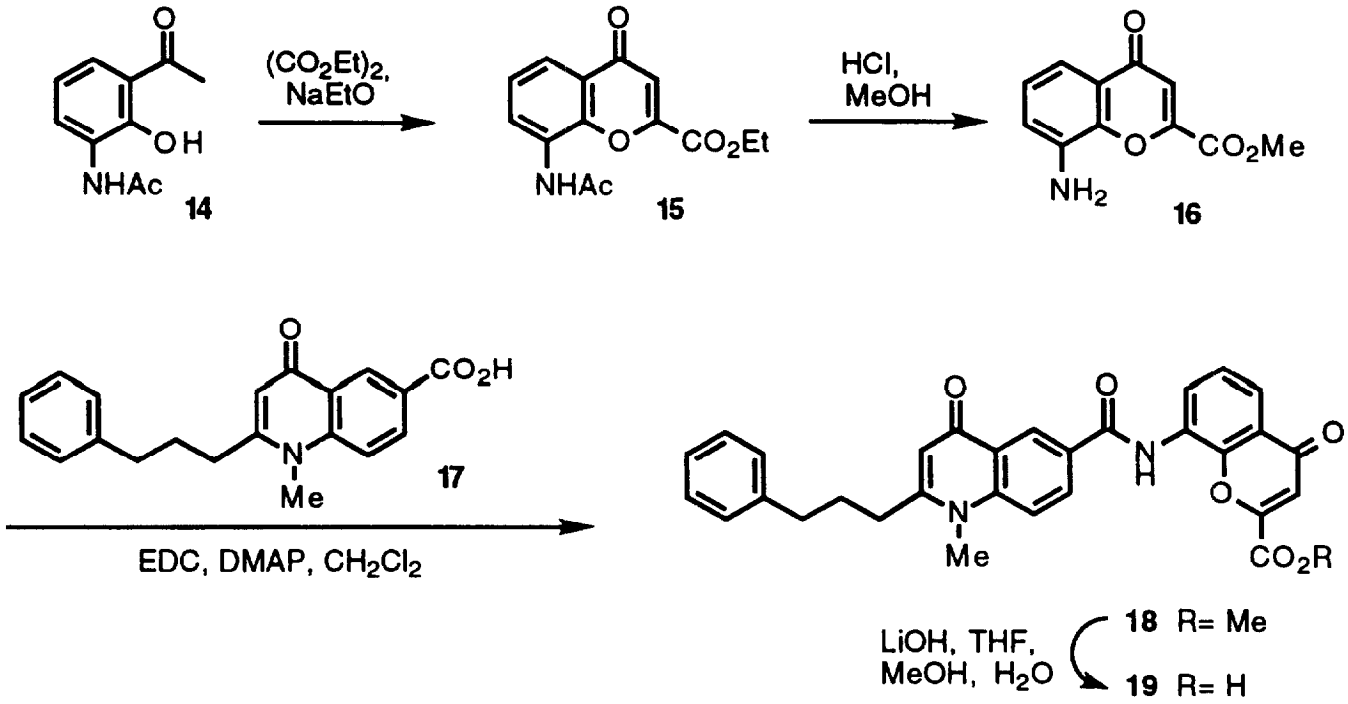
Scheme 5. Preparation of compounds **13c–j**.

At this point in the synthesis, the procedure followed was the same for both *N*-benzyl and *N*-methyl series (schemes 4, 5). Reduction of nitrocompounds **9a–b**, **8e–o** by catalytic hydrogenation with Pd/charcoal or using ammonium formate catalysed with Pd/charcoal gave the aminoderivatives **10a–b**, **10c–i** except for **8k** where cleavage of the *N*-benzyl group occurred at the same time as that of the reduction of the nitro group, affording the *N*-unsubstituted 6-amino-2-methyl-4-oxo-1,4-dihydroquinoline. The reduction of the nitro group of **8k** and **8o** to give **10g** and **10i** respectively was achieved using $SnCl_2$ in ethanol without problems of debenzylation. Acylation of aminoderivatives **10c–e** to **11c–e** was achieved by reaction with cyclopentylacetic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) and 4-dimethylaminopyridine (DMAP) in methylene chloride solution. Alkyloxycarbonylation of **10a, b, e–i** with cyclopentyl chloroformate using *N*-methylmorpholine as a base in methylene chloride solution afforded carbamates **11a, b, f–j** in acceptable yields. Saponification of **11a–j** with LiOH in aqueous methanol at room temperature was conducted selectively to afford the acids **12a–j**, which were condensed with *o*-toluenesulfonamide in the presence of DMAP and EDC in dry methylene chloride solution, yielding the compounds **13a–j**. The target compound **13k** was obtained from **8g** following the same synthetic route, but avoiding the reduction step of the nitro group and following the introduction of the lipophilic chain on the resulting amino group.

The amino derivative **16** was obtained from the 2-hydroxyacetophenone **14** [30] (scheme 6) by Claisen condensation with diethyl oxalate followed by acid cyclization. Deprotection of the amino group and transesterification occurred during the acid treatment. Condensation of the aminochromone **16** with the acid **17** using EDC as the activating agent in the presence of DMAP in methylene chloride as a solvent yielded the amide **18**. Chemoselective saponification of the ester group of **18** to produce **19** was carried out using soft basic conditions to prevent amide hydrolysis and chromone opening. Thus, treatment of **18** with a dilute lithium hydroxide solution gave the desired quinolone derivative **19** in 74% yield.

Pharmacology

The ability of compounds **4a,b**, **13a–k**, and **19** to compete with the ^{3}H-LTD$_4$ binding to guinea pig lung membranes in vitro was evaluated and inhibition constants (K_i) were calculated. Alternatively, the ability of compounds to antagonise LTD$_4$-induced contractions of isolated guinea pig ileum was also evaluated (table I).



Scheme 6. Preparation of compounds **18** and **19**.

Table I. Biological activities of the investigated compounds[a].

Compound	*LTD_4 binding K_i (nM)*[b]	*Guinea pig ileum IC_{50} (nM)*[c]
ICI-204219	0.5 ± 0.1	5
ONO-1078	0.33 ± 0.1	0.61
RG-12553[d]	16.1 ± 1.4	32
13a	>1000	>100
13b	372 ± 14	100
13c	>1000	>100
13d	>1000	>100
13e	18 ± 6	4
13f	16 ± 2	7
13g	>1000	>100
13h	9.4 ± 4	6
13i	>1000	>100
13j	>1000	>100
13k	>1000	>100
19	>1000	>100
4a	752 ± 16	>100
4b	232 ± 1	>100

[a]For reference compound structures see figure 1, table V and schemes 2 and 4. [b]Inhibition constant for displacement of ^{3}H-LTD_4 in guinea pig lung membranes. K_i values are the mean of five experiments conducted individually. [c]IC_{50} value on LTD_4-induced contraction on guinea pig ileum (myenteric plexus). [d]Corresponds to the acid analog of compounds **RG-12553** (see fig 1).

Molecular modelling

The molecular modelling study sought to predict the activity of the compounds proposed for synthesis and to rationalise the relationship between chemical structure and the activity results. The seven-point pharmacophore and CoMFA models used as prediction tools have been described previously [31]. Therefore, here we shall restrict ourselves to a brief description with some comments regarding the method utilised.

The LTD_4-receptor binding K_i values (converted to $-\log K_i$ 'pK_i') were used in the molecular modelling study to quantify the biological activity. Activity predictions were made using a combined pharmacophore and CoMFA approach (table II) based on: (1) obtaining the molecule alignments using the pharmacophore hypothesis and the fitting option implemented in Catalyst [32] and (2) the use of these alignments as input for CoMFA to predict activities [33]. As a result of this work, we predicted the activity for compounds **13a–j** that are structurally related to **ICI-204219**. The 'learning' set of compounds used to derive the pharmacophore and CoMFA models initially included the lead compounds **ICI-204219**, **ONO-1078** and **RG-12553** (fig 1) [9, 34]. The compounds structurally related to **ICI-204219** were retained in the final CoMFA model, whereas the process of compound selection required the rejection of **ONO-1078**. Therefore, in the present study we only considered the activity prediction of compounds **13a–j** that were structurally related to **ICI-204219**.

The pharmacophore hypothesis consists of seven chemical features: an acidic or negative ionizable function, a hydrogen-bond acceptor (HBA) and five hydrophobic regions. The model is shown in figure 2 with compounds **13e** and **ICI-204219** fitted. The chemical features are drawn as spheres. Only HBA is depicted using two spheres due to the directional nature of its chemical function [35]. Molecule alignments were obtained based on the collection of conformers generated for each molecule within Catalyst and the pharmacophore hypothesis. Moreover, several alignments could be obtained per molecule using the fitting tools within the programme (rigid fit). Then 1–2 alignments were selected per molecule, taking into consideration criteria of low conformational energy and optimum overall superposition onto **ICI-204219**. The molecule alignments on the pharmacophore were used as input for CoMFA and the corresponding CoMFA model was derived, selecting the compound and conformers on the basis of Q^2-improvement criteria. The final CoMFA model presented the following correlation parameters: $Q^2 = 0.794$, $S_{PRESS} = 0.376$ (optimum number of components 4), conventional $P^2 = 0.987$, with a standard error of estimate of 0.095.

The combined pharmacophore–CoMFA approach was used to predict the activity of compounds **13a–j** (table II). As in the process for obtaining the models, activity prediction comprises an initial alignment selection followed by prediction. In the learning set of compounds, alignments were chosen for each proposed structure from among the collection of pharmacophore alignments proposed by Catalyst. Selection was based on criteria of low conformational energy and optimum overall superposition onto the conformers of **ICI-204219**. Although we intended to select one conformer alignment per compound, the process led to two to three candidate conformers for **13e,i,j** and **h**. Once the conformer alignments had been chosen, antagonist $-\log K_i$ values were predicted using the CoMFA 3-D-QSAR model described above (see *Experimental protocols* for details).

Activity predictions for compounds **13a–j** are summarised in table II and figure 3. On the whole, activity was accurately estimated for compounds which were highly active ($K_i^{exp} < 500$ nM), ie **13b,e,f** and **h**, while the inactive compounds **13a,c,d,g,i** and **j** ($K_i^{exp} > 1000$ nM) were largely overestimated. Although all these low-active compounds were superimposed onto the pharmacophore, the inaccurate

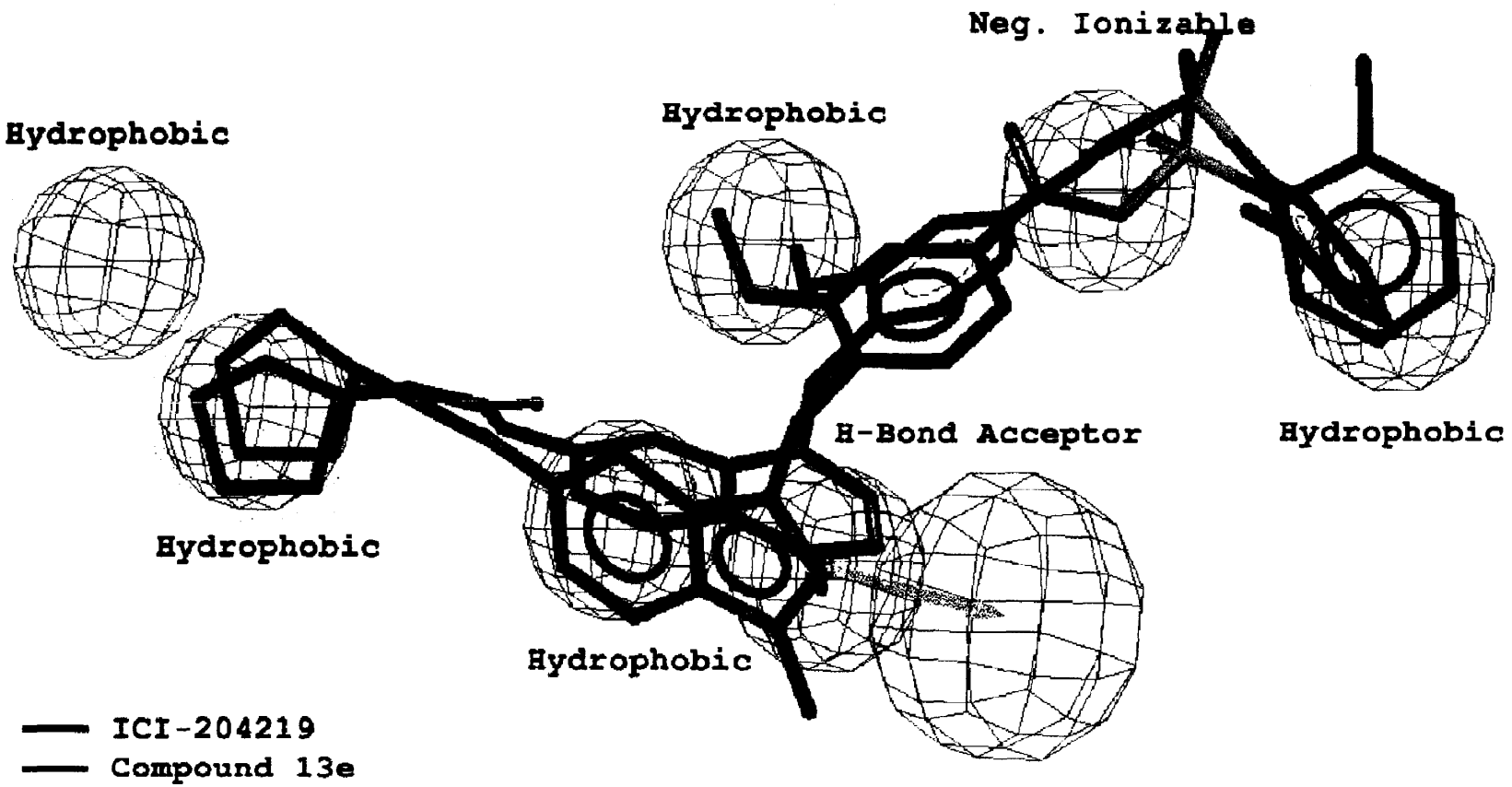


Fig 2. Pharmacophore model with compounds **13e** and **ICI-204219** fitted [31]. The pharmacophore consists of seven chemical features: an acidic or negative ionizable function, a hydrogen-bond acceptor and five hydrophobic regions. The chemical features are drawn as globes. Only HBA is shown by two globes due to the directional nature of this chemical function [35].

Table II. Observed vs predicted pK_i values (^{3}H-LTD$_4$ binding) for compounds **13a–k** structurally related to **ICI-204219**.

Compound[a]	*Exp values*		*Estimated values*		
	K_i	pK_i[b]	pK_i[c]	*Mean*[c,d]	*SD*[c,d]
ICI-204219	0.50	9.30	9.57/9.50	9.53	0.049
13a	>1000	6.00	7.42	7.42	–
13b	372	6.42	7.58	7.58	–
13c	>1000	6.00	8.03	8.03	–
13d	>1000	6.00	8.08	8.08	–
13e	18	7.74	8.33/7.01/7.63	7.65	0.66
13f	16	7.79	8.79	8.79	–
13g	>1000	6.00	7.60	7.60	
13h	9.4	8.02	7.95/8.76	8.35	0.57
13i	>1000	6.00	7.16/7.16	7.16	0.00
13j	>1000	6.00	6.95/7.24	7.00	0.21
13k	>1000	6.00	nm[e]	–	–

[a]Compound **ICI-204219** was present in the learning set of compounds used to derive the CoMFA model and is included in this table as reference; [b]for ease of comparison, the –log (K_i) 'pK_i' values are tabulated; [c]predicted values of activity 'pK_i' based on the non-cross-validated CoMFA analysis described in the text; compounds with multi-conformational models require each conformer to be determined independently; [d]estimated pK_i mean and standard deviation values for the compounds with multiple conformations; [e]nm: no mapping: compound **13k** did not properly map the pharmacophore, and therefore could not be estimated.

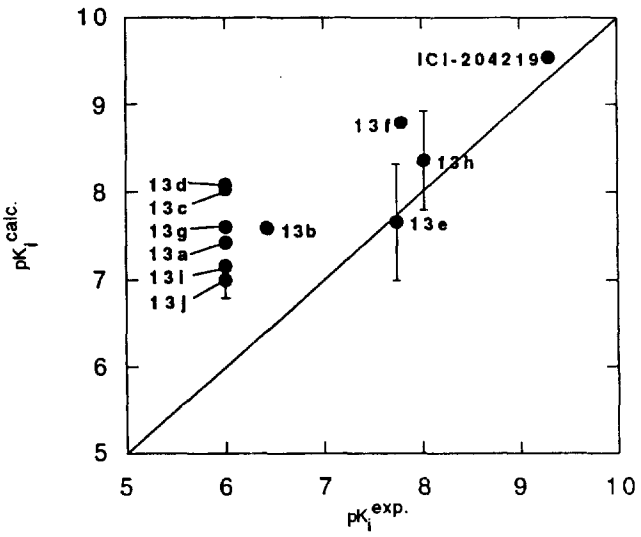


Fig 3. Observed vs predicted pK_i values for compounds **13a–j**, structurally related to **ICI-204219**. For compounds with several conformers, mean values are shown with bars illustrating the range of predicted activity.

predictions obtained could be caused by inadequate alignment, ie, activity is overestimated for inactive molecules when they are forced to align. In general, compounds having the correct substitution in the quinolone ring (1,7- and 2,7-substitutions), mimicking the 3,5-substituted indole of **ICI-204219**, overlay well on the pharmacophore and are expected to be active (ie, **13b** (372 nM), **13e** (18 nM), **13f** (16 nM) and **13h** (9.4 nM)). Moreover, a central hydrophobic interaction mapping onto the methoxy group of most compounds of the series is likely to be important for activity. The effect has been observed when compounds lacking this methoxy group were shown to be inactive (**13i–j**).

Results and discussion

The aim of this paper is to study the use of suitably substituted 4-quinolone systems as a template to replace different moieties in potent LTD$_4$ antagonists such as **ICI-204219**, **ONO-1078** or **RG-12553**. Three general structures (**A**, **B**, and **C**; fig 1) were tested in which the 4-quinolone system replaced the chromone heterocycle, the indole nucleus and the central phenyl

ring in the prototype antagonists. The activity results demonstrated that the 4-quinolone system can only effectively replace the indole nucleus in the ICI compound. In contrast, the activity was completely lost when a 2,7-disubstituted 4-quinolone system (compounds **4a** and **b**) was used to replace the 2,7-disubstituted chromone nucleus in compound **RG-12553**. Likewise, the activity was also absent when the central phenyl ring in the ONO prototype was replaced by a 2,6-disubstituted 4-quinolone nucleus, compound **19**.

In the series of compounds structurally related to **ICI-204219**, the 4-quinolone system is valid as a chemical template only if the quinolone substituents are suitably positioned. This is evident when comparing the good activity of the 1,7-isomers **13e** and **f** in vitro, with the weak activity shown by the 2,7-isomer (**13b**) or with the total inactivity shown by the 1,5 and the 1,6-isomers **13d** and **c** respectively. This observation suggests that an adequate geometric pattern is an important prerequisite for activity, and that the central bicycle (4-quinolone or indole) acts purely as a chemical template orienting the functional groups essential for activity. In support of this, we observed that the bicyclic system simply maps a central hydrophobic feature in the pharmacophore (fig 2), and accordingly Matassa et al reported the equivalence of the indole ring with several alternative bicyclic aromatics [36].

Additional observations support the relevance of geometric distribution. Methyl substitution in positions 2 and 3 of the quinolone ring produces different effects on activity. While 3-methyl substituted compound **13h** retains activity, compound **13g**, with the methyl substitution in position 2 of the ring, is inactive. This behaviour can be analysed in terms of the steric contact between the methyl and methoxy groups. While there is a steric hindrance in **13g** (2-CH_3), it is absent in **13h** (3-CH_3), and therefore a different geometry of the predominant conformations is induced. Accordingly, we also observed significant differences between these compounds both in the NMR spectra (see above) and the distribution of conformations (results on conformational analysis not shown).

In this series, the methoxy substituent in the central phenyl ring together with the lipophilic group (cyclopentylacetamide or cyclopentylcarbamate) substituted in position 7 of the quinolone ring are crucial for activity. Compounds lacking the methoxy group have shown to be inactive (**13i, j**). Furthermore, the compound with a nitro group in position 7 of the quinolone ring (**13k**) is inactive compared to **13e** or **f**, which have a lipophilic cyloalkyl chain. In this lipophilic moiety cyclopentylcarbamate and cyclopentylacetamide present the same potency in vitro. Accordingly, the pharmacophore shown in figure 2 incorporates lipophilic chemical features mapping this methoxy group and the lipophilic cyclopentyl group essential for activity.

These novel 4-quinolone derivatives **13e** and **f** have been selected for further pharmacological evaluation; they are an interesting starting point from which to develop new LTD_4 antagonist series.

Experimental protocols

Molecular modelling

All molecular modelling studies were performed on a Silicon Graphics Personal IRIS 4D35 computer, running Catalyst software version 2.2 (Molecular Simulations Inc, San Diego, CA) and SYBYL software version 6.1 (Tripos Associates, St Louis, MO). The basic modelling methods (eg, conformational analysis, molecule fitting, etc) were performed within the programme Catalyst [35] using the implemented chemical features and the energy minimisation procedure with a standard conjugate gradients minimisation algorithm and a modified version of CHARMm molecular mechanics force field [37]. Conformational analysis was performed as implemented in the programme using the minimiser described above coupled to a 'poling' function to assess conformational variation [38, 39] and the BEST algorithm which seeks to optimise the conformational coverage versus the size of the assembly [40]. In the calculation, a threshold of 250 conformers per molecule with a maximum of 20 kCal/mol was used. The fitting of a molecule into a given pharmacophore is performed within Catalyst by taking into account the chemical features present in the molecule. The library of chemical descriptors within the programme [35] was used to map the chemical functionalities in each molecule, then fitting operations were undertaken using the FAST algorithm which does not alter the geometry of the molecule (rigid fit). The pharmacophore used in molecule alignment is shown in figure 2 and has previously been described in detail [31]. Given the collection of conformers considered, several alignments on the pharmacophore model are expected for each molecule. Within this collection, 1-3 were selected on the basis of their having low conformational energy and their optimum overall superposition onto **ICI-204219**. The molecules aligned in the pharmacophore were used for activity prediction using the CoMFA model. The CoMFA model used is shown in figure 2, and has previously been described in detail [31]. On the set of molecule alignments selected we ran the general CoMFA model in prediction mode [33]. For the CoMFA calculations, the steric and electrostatic interactions were determined using the TRIPOS force field using a C_{sp^3} probe with a charge of +1. Atomic charges were obtained on the ionized form of the molecules using MOPAC 6.0 (MNDO). A standard CoMFA lattice was used with a 2Å grid spacing. In the case where both fields were used (steric and electrostatic), the CoMFA analyses were performed with the contributions scaled according to the standard CoMFA deviations as implemented in the programme.

Chemistry

All melting points were determined in a capillary tube on a Gallenkamp melting point apparatus and are uncorrected. ^1H- and ^{13}C-NMR spectra were recorded on a Varian XL-200 spectrometer, Varian XL-300 spectrometer or on a VXR-500

instrument using TMS as internal standard. Signal multiplicities are represented by s (singlet), d (doublet), t (triplet), q (quadruplet), brs (broad singlet), and m (multiplet). Chemical shifts are reported in ppm downfield (δ) from TMS as internal standard; *J* values are given in Hz. IR spectra were recorded with a Nicolet 205 spectrophotometer and only noteworthy absorption levels (reciprocal centimetres) are listed. Low resolution mass spectra were determined on a Hewlett–Packard 5930A mass spectrometer. Microanalyses were carried out on a Carlo Erba Fisons EA-1108 by the Servicio Científico Técnico de la Universidad de Barcelona; they were performed for C, H, N or C, H, N, S and results were within ± 0.4% of theoretical values. TLC was carried out on SiO_2 (silica Gel 60 F254, Merck 0.063–0.200 mm); the spots were located with iodoplatinate reagent or UV light. Column chromatography was carried out on SiO_2 (silica gel 60, SDS: 0.060–0.2 mm). Flash chromatography was carried out on SiO_2 (silica gel 60, SDS: 0.040– 0.060 mm).

N-*Acetyl-3-benzyloxyaniline.* A mixture of benzyl chloride (3.27 mL, 28 mmol), 3-acetamidophenol (5.1 g, 33.6 mmol) and dry potassium carbonate (8.9 g, 64 mmol) in dry acetone (50 mL) was stirred and refluxed for 8 h. The solvent was evaporated and the residue was dissolved in water and extracted with ether (3 x 30 mL). The organic layer was washed with 10% aqueous sodium hydroxide, brine, dried over potassium carbonate and evaporated to give *N*-acetyl-3-benzyloxyaniline (5.86 g, 74%); IR ($CHCl_3$): 1688 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.11 (s, 3H); 4.98 (s, 2H); 6.72 (dd, *J* = 8.1 and 1.8 Hz, 1H); 7.03 (d, *J* = 8.1 Hz, 1H); 7.21 (dd, *J* = 8.1 and 8.1 Hz, 1H); 7.32–7.38 (m, 6H); 8.20 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 25.0 (q); 70.4 (t); 107.2 (d); 111.4 (d); 113.0 (d); 128.0 (d); 128.5 (2d); 129.0 (2d); 130.2 (d); 137.3 (s); 139.8 (s); 159.7 (s); 169.6 (s); MS *m/z* 242 (M+1, 5); 241 (M^+, 25); 91 (100); 65 (22).

N-*Acetyl*-N-*methyl-3-benzyloxyaniline.* Lithium diisopropylamide (14.2 mL, 21.4 mmol) was added to a stirred solution of *N*-acetyl-3-benzyloxyaniline (4.3 g, 17.8 mmol) in dry tetrahydrofuran (200 mL) cooled at –78 °C under nitrogen and the mixture was stirred for 30 min. Iodomethane (3.3 mL, 53.4 mmol) was added and the mixture was stirred at room temperature for 2 h. The solvent was evaporated to afford a residue which was purified by column chromatography. Elution with hexane/dichloromethane (60:40) gave *N*-acetyl-*N*-methyl-3-benzyloxyaniline (4.4 g, 98%); IR ($CHCl_3$): 1645 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.86 and 2.17 (2s, 3H); 3.25 (s, 3H); 5.06 (s, 2H); 6.77–6.80 (m, 2H); 6.86–6.98 (m, 1H); 7.27–7.43 (m, 6H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 22.2 and 24.4 (q); 36.9 (q); 70.0 (t); 113.8 (d); 113.9 (d); 119.3 (d); 127.3 (2d); 128.0 (d); 128.5 (2d); 130.3 (d); 136.2 (s); 145.4 (s); 159.4 (s); 170.4 (s); MS *m/z* 256 (M+1, 2); 255 (M^+, 7); 91 (100).

N-*Methyl-3-benzyloxyaniline.* A solution of *N*-acetyl-*N*-methyl-3-benzyloxyaniline (6.5 g, 25.6 mmol) and potassium hydroxide (14.3 g, 256 mmol) in methanol (600 mL) was refluxed during 12 h. The solvent was evaporated and the residue was dissolved in water and extracted with ether. The organic layer was washed with water, dried over Na_2SO_4, and evaporated to afford *N*-methyl-3-benzyloxyaniline (5 g, 91%); IR (NaCl): 3415 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.76 (s, 3H); 3.68 (brs, 1H); 5.01 (s, 2H); 6.21–6.37 (m, 3H); 7.04–7.12 (m, 1H); 7.29–7.43 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 30.6 (q); 69.7 (t); 99.2 (d); 103.0 (d); 105.9 (d); 127.4 (2d); 127.8 (d); 128.4 (2d); 129.8 (d); 137.2 (s); 150.6 (s); 160.0 (s); MS *m/z* 213 (M+1, 30); 214 (M^+, 4); 91 (100).

*Dimethyl 2-(*N*-methyl-3-benzyloxyanilino)butendioate* ***1a***. Benzyltrimethylammonium hydroxide (Triton B, 40% methanol solution, 3.6 mmol) was added to a stirred solution of *N*-methyl-3-benzyloxyaniline (3.1 g, 14.5 mmol) and dimethyl acetylenedicarboxylate (3.1 g, 14.5 mmol) in methanol (100 mL) at room temperature and the reaction mixture was refluxed for 6 h. The solvent was removed in vacuo to afford a brown oil which was purified by column chromatography. Elution with hexane/dichloromethane (70:30) gave **1a** (4.1 g, 79%); IR (NaCl): 1750, 1617 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.22 (s, 3H); 3.67 (s, 3H); 3.72 (s, 3H); 4.63 (s, 1H); 5.05 (s, 2H); 6.80–6.93 (m, 3H); 7.23–7.45 (m, 6H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 40.1 (q); 50.6 (q); 53.1 (q); 70.6 (t); 89.0 (d); 113.4 (d); 114.5 (d); 119.2 (d); 128.0 (2d); 128.6 (d); 129.1 (2d); 130.6 (d); 136.9 (s); 146.1 (s); 154.2 (s); 159.9 (s); 168.1 (s); 169.0 (s); MS *m/z* 356 (M+1, 1); 355 (M^+, 4); 91 (11).

Dimethyl 2-(3-hydroxyanilino)butendioate ***1b***. Benzyltrimethylammonium hydroxide (Triton B, 40% methanol solution, 35 mmol) was added to a stirred solution of 3-aminophenol acetate (21.0 g, 139 mmol) and dimethyl acetylenedicarboxylate (20.0 g, 139 mmol) in methanol (300 mL) at room temperature and the reaction mixture was refluxed for 6 h. The solvent was removed in vacuo to afford a brown oil, which was purified by column chromatography. Elution with hexane/dichloromethane (70:30) gave dimethyl 3-acetoxyanilinobutendioate as a *Z,E* isomer mixture (700 mg, 17%); IR ($CHCl_3$): 3021, 1725, 1700, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.10 (s, 3H); 2.13 (s, 3H); 3.68 (s, 3H); 3.72 (s, 3H); 3.74 (s, 3H); 3.91 (s, 3H); 5.20 (s, 1H); 6.58 (s, 1H); 6.60–6.70 (m, 1H); 7.20–7.40 (m, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 24.3 (q); 52.0 (q); 53.1 (q); 99.0 (d); 107.7 (d); 111.2 (d); 114.6 (d); 115.1 (d); 129.7 (d); 139.6 (s); 149.7 (s); 156.7 (s); 169.1 (s); MS *m/z* 294 (M+1, 1); 293 (M^+, 6); 191 (100). Elution with hexane/dichloromethane (50:50) gave **1b** as *Z,E* isomer mixture (26 g, 74%); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.70 (s, 3H); 3.72 (s, 3H); 3.73 (s, 3H); 3.75 (s, 3H); 5.38 (s, 1H); 6.38 (s, 1H); 6.39–6.40 (m, 2H); 6.50–6.59 (m, 1H); 7.02–7.14 (m, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 51.3 (q); 52.9 (q); 93.5 (s); 103.5 (s); 107.8 (d); 111.5 (d); 112.4 (d); 130.0 (d); 141.2 (s); 147.2 (s); 156.9 (s); 165.1 (s); 169.9 (s).

Methyl 2-methyl-3-(3-nitroanilino)propenoate ***1c***. A mixture of 3-nitroaniline (852 mg, 6.2 mmol), methyl 2-methyl-3,3-dimethoxypropionate (1 g, 6.2 mmol) and *p*-toluenesulfonic acid (1 mg, 5.2 x 10^{-3} mmol) in benzene (50 mL) was refluxed for 16 h. The cold solution was washed with aqueous sodium bicarbonate solution, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography. Elution with hexane/dichloromethane (50:50) gave **Z-1c** (530 mg) as a yellow solid; mp = 110–112 °C (from dichloromethane); IR (KBr): 1680, 1527, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.87 (s, 3H); 3.77 (s, 3H); 7.15 (d, *J* = 11.8 Hz, 1H); 7.18 (d, *J* = 7.7 Hz, 1H); 7.41 (dd, *J* = 9.7 and 7.7 Hz, 1H); 7.73–7.76 (m, 2H); 10.01 (d, *J* = 11.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 15.6 (q); 51.0 (q); 97.8 (s); 108.3 (d); 115.6 (d); 120.6 (d); 130.1 (d); 138.6 (d); 142.1 (s); 149.1 (s); 170.3 (s); MS *m/z* 237 (M+1, 14); 236 (M^+, 100); 204 (63); 175 (39); 159 (44); anal $C_{11}H_{12}N_2O_4$ (C, H, N). The subsequent fractions gave ***E-1c*** (205 mg), total yield 67%; mp = 149–151 °C (from dichloromethane); IR (KBr): 1669, 1528, 1348 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.89 (s, 3H); 3.78 (s, 3H); 6.30 (d, *J* = 12.5 Hz, 1H); 7.26 (dd, *J* = 8.1 and 1.7 Hz, 1H); 7.46 (dd, *J* =

8.3 and 8.1 Hz, 1H); 7.79–7.82 (m, 2H); 7.88 (d, J = 12.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 9.7 (q); 51.4 (q); 101.6 (s); 109.5 (d); 115.8 (d); 120.5 (d); 130.2 (d); 136.4 (d); 142.7 (s); 149.1 (s); 169.6 (s); MS *m/z* 237 (M+1, 16); 236 (M^+, 100); 204 (74); 175 (44); 159 (51); anal $C_{11}H_{12}N_2O_4$ (C, H, N).

Methyl 5-hydroxy-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylate ***2a*** *and methyl 7-hydroxy-1-methyl-4-oxo-1,4-dihydroquinoline-2-carboxylate* ***2b***. A solution of **1a** (1.2 g, 3.3 mmol) in polyphosphoric acid (17 g, 50 mmol) was heated at 80 °C for 2 h. The reaction mixture was poured into water, neutralized with aqueous ammonium hydroxide solution and extracted with ethyl acetate. The organic layer was washed with water, then dried, and evaporated to afford a residue which was purified by flash column chromatography. Elution with ether/acetone/diethylamine (95:5:2) gave **2b** (220 mg, 28%); IR ($CHCl_3$): 1717, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.91 (s, 3H); 3.90 (s, 3H); 6.38 (d, J = 2.3 Hz, 1H); 6.46 (dd, J = 8.9 and 2.3 Hz, 1H); 6.50 (s, 1H); 7.91 (d, J = 8.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 30.0 (q); 52.8 (q); 97.4 (d); 105.9 (s); 110.8 (d); 111.9 (d); 127.5 (d); 142.8 (s); 152.8 (s); 156.9 (s); 160.8 (s); 164.8 (s); MS *m/z* 234 (M+1, 14); 233 (M^+, 100); 91 (20). The subsequent fractions gave **2a** (236 mg, 31%); IR ($CHCl_3$): 3000, 1738, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.81 (s, 3H); 4.02 (s, 3H); 6.55 (s, 1H); 6.77 (d, J = 8.2 Hz, 1H); 6.87 (d, J = 8.7 Hz, 1H); 7.56 (dd, J = 8.7 and 8.2 Hz, 1H); 14.26 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 38.0 (q); 53.7 (q); 104.8 (d); 110.2 (d); 110.7 (d); 135.1 (d); 162.1 (s); 182.4 (s); MS *m/z* 234 (M+1, 9); 233 (M^+, 67); 205 (13); 160 (22).

General procedure for preparation of quinolones ***2c–h*** and ***2j–k***

A solution of **1b–c** or **6a–c** (1 mmol) in diphenyl ether (2 mL) was refluxed for 20 min under nitrogen. Hexane (10 mL) was added to the cold solution and the resulting mixture was poured into a flash column chromatography with silica gel.

Methyl 7-hydroxy-4-oxo-1,4-dihydroquinoline-2-carboxylate ***2c*** [41]. Following the above general procedure compound **2c** was obtained by elution with hexane/dichloromethane (25:75). Yield 46%; mp = 131–133 °C (from chloroform); IR (KBr): 3423, 3332, 1739, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.97 (s, 3H); 4.28 (brs, 1H); 6.57–6.63 (m, 3H); 8.01 (d, J = 9.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 53.4 (q); 100.5 (d); 106.9 (s); 111.3 (d); 113.4 (d); 129.0 (d); 145.3 (s); 155.1 (s); 158.3 (s); 163.4 (s); 166.3 (s); MS *m/z* 220 (M+1, 14); 219 (M^+, 100); 191 (75); 160 (39); 104 (63); anal $C_{11}H_9NO_4$ (C, H, N).

6-Nitro-4-oxo-1,4-dihydroquinoline ***2d*** *[24].* Following the above general procedure, compound **2d** was obtained by elution with dichloromethane/methanol (95:5). Yield 58%; IR (KBr): 1647, 1501, 1339 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 6.47 (d, J = 7.5 Hz, 1H); 7.82 (d, J = 9.2 Hz, 1H); 8.13 (d, J = 7.5 Hz, 1H); 8.57 (dd, J = 9.2 and 2.6 Hz, 1H); 9.18 (d, J = 2.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 50 MHz) δ: 110.4 (d); 120.3 (d); 121.8 (d); 124.9 (s); 125.9 (d); 140.9 (d); 142.7 (s); 143.9 (s); 176.6 (s); MS *m/z* 191 (M+1, 6); 190 (M^+, 40); 160 (13); 116 (31); 111 (15); 89 (36); 57 (100).

5-Nitro-4-oxo-1,4-dihydroquinoline ***2e*** *and 7-nitro-4-oxo-1,4-dihydroquinoline* ***2f*** *[43].* Following the above general procedure by elution with dichloromethane/methanol (95:5) a mixture of **2e** and **2f** was obtained; yield 66%.

2-Methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***2g*** *and 2-methyl-7-nitro-4-oxo-1,4-dihydroquinoline* ***2h***. Following the above general procedure by elution with dichloromethane/methanol (97:3) a mixture of **2g** and **2h** was obtained; yield 57%.

3-Methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***2j*** *and 3-methyl-7-nitro-4-oxo-1,4-dihydroquinoline* ***2k***. Following the above general procedure by elution with dichloromethane/methanol (95:5) a mixture of **2j** and **2k** was obtained; yield 51%.

Methyl 4-oxo-2-(3-phenylpropyl)-1,4-dihydroquinoline-6-carboxylate ***2i***. A solution of **5c** (4.0 g, 12.5 mmol) and methyl 4-aminobenzoate (1.9 g, 12.5 mmol) in diphenyl ether (45 mL), was heated at 140 °C for 45 min and then refluxed for 2 h under nitrogen. Hexane (50 mL) was added to the cold solution, the precipitate was collected by filtration and washed with hexane (2 x 30 mL) to afford **2i** (5.13 g, 57%); mp = 219–221 °C (from dichloromethane); IR (KBr): 3570, 1725, 1660, 1549 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 2.05–2.14 (m, 2H); 2.70–2.78 (m, 4H); 3.94 (s, 3H); 6.33 (s, 1H); 7.25–7.36 (m, 5H); 7.69 (d, J = 8.8 Hz, 1H); 8.32 (dd, J = 8.8 and 2.1 Hz, 1H); 8.98 (d, J = 2.1 Hz, 1H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 31.6 (t); 34.5 (t); 36.2 (t); 52.8 (q); 109.9 (d); 119.5 (d); 127.1 (d); 128.8 (d); 129.3 (s); 129.5 (2d); 131.5 (2d); 133.2 (d); 142.3 (s); 144.3 (s); 157.6 (s); 180.4 (s); MS *m/z* 322 (M+1, 1); 321 (M^+, 2); 217 (100); anal $C_{20}H_{19}NO_3$•0.5 CH_2Cl_2 (C, H, N).

General procedure for preparation of quinolones ***2l–n***

Iodomethane (10 mmol) was added to a stirred solution of the corresponding nitro-4-quinolone **2d–f** (1 mmol) and potassium hydroxide (3 mmol) in methanol (15 mL). The mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure and the residue purified by column chromatography.

1-Methyl-6-nitro-4-oxo-1,4-dihydroquinoline ***2l*** *[44].* Elution with dichloromethane gave **2l** (1.13 g, 82%); mp = 234–235 °C (from dichloromethane) (Lit [44] 236–237 °C); IR (KBr): 1640, 1335 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.91 (s, 3H); 6.35 (d, J = 7.8 Hz, 1H); 7.58 (d, J = 9.3 Hz, 1H); 7.67 (d, J = 7.8 Hz, 1H); 8.48 (dd, J = 9.34 and 2.7 Hz, 1H); 9.22 (d, J = 2.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 41.0 (q); 111.5 (d); 116.9 (d); 123.4 (d); 126.2 (s); 126.4 (d); 143.4 (s); 143.8 (s); 145.1 (d); 177.6 (s); MS *m/z* 205 (M+1, 13); 204 (M^+, 100); 190 (4); 158 (49); 130 (21).

1-Methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***2m*** *and 1-methyl-7-nitro-4-oxo-1,4-dihydroquinoline* ***2n*** *[45].* Elution with ether/acetone/diethylamine (70:30:5), gave **2n** (1.3 g, 41%); IR (NaCl): 1596, 1342 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.91 (s, 3H); 6.35 (d, J = 7.8 Hz, 1H); 7.64 (d, J = 7.8 Hz, 1H); 8.16 (dd, J = 8.8 and 1.9 Hz, 1H); 8.34 (d, J = 1.9 Hz, 1H); 8.59 (d, J = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 40.8 (q); 111.0 (d); 111.7 (d); 117.4 (d); 128.6 (d); 129.7 (s); 140.2 (s); 145.7 (d); 149.5 (s); 171.1 (s); MS *m/z* 206 (M+2, 1); 205 (M+1, 13); 204 (M^+, 100); 158 (43). The subsequent fractions gave **2m** (1.2 g, 38%); mp 240-243 °C (from dichloromethane); IR (NaCl): 1638, 1335 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.85 (s, 3H); 6.23 (d, J = 7.8 Hz, 1H); 7.31 (d, J = 7.8 Hz, 1H); 7.54 (m, 2H); 7.70 (d, J = 7.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 45.7 (q); 115.0 (d); 122.2 (d); 122.8 (d); 136.3 (d); 145.6 (s); 177.6 (s); MS *m/z* 206 (M+2, 2); 205 (M+1, 14); 204 (M^+, 100); 158 (18); 130 (35); anal $C_{10}H_8N_2O_3$•0.5 H_2O (C, H, N).

Methyl 1-methyl-4-oxo-2-(3-phenylpropyl)-1,4-dihydroquinoline-6-carboxylate ***2o***. A solution of **2i** (1.1 g, 3.4 mmol) in dry tetrahydrofuran (30 mL) was added to a stirred suspension of oil-free sodium hydride (165 mg, 4.1 mmol) in tetrahydrofuran (5 mL) cooled at 0 °C under nitrogen and the mixture was stirred for 30 min. Iodomethane (2.1 mL, 34.2 mmol) was added and the reaction was heated at 50 °C for 3 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography. Elution with dichloromethane:methanol (99:1) gave **2o** (1.01 g, 93%); mp = 158–159 °C (from dichloromethane); IR (NaCl): 1720, 1638, 1598 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.95–2.08 (m, 2H); 2.62–2.80 (m, 4H); 3.62 (s, 3H); 3.92 (s, 3H) ; 6.18 (s, 1H); 7.16–7.32 (m, 5H); 7.43 (d, *J* = 8.8 Hz, 1H) ; 8.17 (dd, *J* = 8.8 and 2.2 Hz, 1H); 8.99 (d, *J* = 2.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 30.4 (t); 34.3 (t); 34.9 (q); 35.5 (t); 52.7 (q); 112.7 (d); 116.1 (d); 125.5 (s); 126.3 (s); 126.9 (d); 128.9 (d); 129.1 (d); 129.6 (d); 133.0 (d); 141.0 (s); 144.5 (s); 155.7 (s); 180.0 (s); MS *m/z* 336 (M+1, 1); 335 (M^+, 3), 231 (100); 144 (10); anal $C_{21}H_{21}NO_3$•0.5 H_2O (C, H, N).

3-(2-Quinolylmethoxy)benzyl methanesulfonate ***3***. Methanesulfonyl chloride (0.54 mL, 7.05 mmol) was added to a stirred solution of 3-hydroxymethylphenyl 2-quinolylmethyl ether [23] (1.25 g, 4.7 mmol) and triethylamine (1.2 mL, 8.46 mmol) in dichloromethane (60 mL) cooled at 0 °C under nitrogen, and the reaction mixture was stirred for 2 h at room temperature. The organic solution was washed with saturated aqueous sodium hydrogen carbonate solution (3 x 50 mL), dried over Na_2SO_4 and evaporated to gave **3** (1.48 g, 91%); ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.87 (s, 3H); 5.20 (s, 2H); 5.39 (s, 2H); 6.95–7.17 (m, 3H); 7.23–7.35 (m, 1H); 7.50–7.85 (m, 4H); 8.08 (d, *J* = 9.5 Hz, 1H); 8.18 (d, *J* = 8.7 Hz, 1H).

1-Methyl-4-oxo-7-[3-(2-quinolylmethoxy)benzyloxy]-1,4-dihydroquinoline-2-carboxylic acid ***4a***. A mixture of **2b** (70 mg, 0.34 mmol) and anhydrous potassium carbonate (93 mg, 0.67 mmol) in dry dimethylformamide (1 mL) under nitrogen was heated at 75 °C for 1.5 h. To the cold mixture a solution of **3** (130 mg, 0.37 mmol) in dry dimethylformamide (1 mL) was added and the reaction mixture was heated at 75 °C for 20 h. The mixture was concentrated under reduced pressure and the residue was dissolved in water (5 mL) and extracted with dichloromethane. The organic layer was washed with 10% aqueous sodium hydroxide solution, brine, and dried over potassium carbonate. Evaporation of the solvent afforded a residue which was purified by flash column chromatography. Elution with dichloromethane/acetone (90:10) gave **4a** (25 mg, 20%); mp = 138–139 °C (from dichloromethane); IR ($CHCl_3$): 1719, 1618 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.93 (s, 3H); 5.36 (s, 2H); 5.43 (s, 2H); 6.46 (d, *J* = 2.4 Hz, 1H); 6.52 (dd, *J* = 8.9, 2.4 and 2.2 Hz, 1H); 6.60 (s, 1H); 7.03–7.13 (m, 2H); 7.29–7.38 (m, 2H); 7.56 (dd, *J* = 8.1 and 7.0 Hz, 1H); 7.68–7.79 (m, 2H); 7.84 (d, *J* = 8.5 Hz, 1H); 8.00 (d, *J* = 8.9 Hz, 1H); 8.10 (d, *J* = 8.4 Hz, 1H); 8.22 (d, *J* = 8.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 30.0 (q); 67.5 (t); 71.3 (t); 97.5 (d); 106.3 (s); 110.9 (d); 112.3 (d); 114.9 (d); 115.0 (d); 119.1 (d); 121.0 (d); 125.5 (d); 127.6 (d); 127.7 (d); 128.6 (s); 128.9 (d); 129.8 (d); 130.0 (d); 136.5 (s); 137.0 (d); 142.5 (s); 147.5 (s); 152.7 (s); 157.0 (s); 157.6 (s); 158.7 (s); 161.3 (s); 164.2 (s); MS *m/z* 467 (M+1, 7); 466 (M^+, 21); 249 (29); 142 (100); anal $C_{28}H_{22}N_2O_5$•H_2O (C. H, N).

4-Oxo-7-[3-(2-quinolylmethoxy)benzyloxy]-1,4-dihydroquinoline-2-carboxylic acid ***4b***. A mixture of **2c** (664 mg, 3.03 mmol) and anhydrous potassium carbonate (1 g, 6.8 mmol) in dry dimethylformamide (5 mL) was heated at 75 °C for 1.5 h under nitrogen. To the cold mixture a solution of **3** (1.3 g, 3.8 mmol) in dry dimethylformamide (5 mL) was added and the solution was heated at 75 °C for 20 h. The solvent was eliminated under reduced pressure, the residue was dissolved in water (25 mL) and extracted with dichloromethane. The organic layer was washed with 10% aqueous sodium hydroxide solution and brine, dried over potassium carbonate and evaporated to afford a residue which was purified by flash column chromatography. Elution with dichloromethane/acetone (95:5), gave **4b** (205 mg, 15%); mp = 188–189 °C (from dichloromethane); IR (KBr): 1722, 1707 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 5.34 (s, 2H); 5.37 (s, 2H); 6.54–6.60 (m, 3H); 7.00–7.09 (m, 2H); 7.28–7.36 (m, 2H); 7.55 (dd, *J* = 8.0 and 7.0 Hz, 1H); 7.66–7.77 (m, 2H); 7.83 (d, *J* = 8.0 Hz, 1H); 7.91 (d, *J* = 8.4 Hz, 1H,); 8.04 (d, *J* = 8.2 Hz, 1H); 8.23 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 67.4 (t); 70.6 (t); 100.2 (d); 111.7 (d); 112.3 (d); 114.8 (d); 114.9 (d); 119.0 (d); 121.0 (d); 126.6 (d); 127.5 (s); 127.6 (d); 127.7 (d); 128.0 (d); 128.1 (d); 129.9 (d); 136.3 (s); 137.5 (d); 143.0 (s); 146.9 (s); 151.8 (s); 156.4 (s); 157.4 (s); 158.4 (s); 161.8 (s); 164.0 (s); MS *m/z* 453 (M+1, 1); 452 (M^+, 12); 281 (13); 142 (100); anal $C_{27}H_{20}N_2O_5$•1.5 H_2O (C, H, N).

2,2-Dimethyl-5-(1-methylthio-4-phenylbutylidene)-1,3-dioxane-4,6-dione ***5c***. A solution of 4-bromopropylbenzene (7 g, 20.2 mmol) in tetrahydrofuran (15 mL) was added to a mixture of magnesium (15 g) in tetrahydrofuran (50 mL) under nitrogen, the mixture was refluxed for 2 h, tetrahydrofuran (40 mL) was added and the reaction mixture was cooled at 0 °C. 2,2-Dimethyl-5-(bismethylthiomethylidene)-1,3-dioxane-4,6-dione [42] (5 g, 20.2 mmol) in tetrahydrofuran (70 mL) was added and the mixture was stirred for 1 h at room temperature under nitrogen. The magnesium was separated by filtration, 5% aqueous hydrochloric acid (30 mL) was added to the filtrate, the mixture was stirred for 10 min and extracted with dichloromethane. The resulting organic solution was dried over Na_2SO_4 and evaporated. The product was purified by column chromatography. Elution with hexane/dichloromethane (70:30) gave **5c** (4 g, 60%); mp = 133–134 °C (from dichloromethane/diisosopropyl ether); IR (KBr): 1701, 1487, 1266 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.69 (s, 6H); 1.94–2.01 (m, 2H); 2.20 (s, 3H); 2.82 (t, *J* = 7.0 Hz, 2H); 3.07–3.12 (m, 2H); 7.18–7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 16.0 (q); 27.5 (q); 32.1 (t,); 34.2 (t); 36.2 (t); 103.8 (s); 126.8 (d); 128.9 (s); 129.0 (2d); 129.1 (2d); 141.5 (s); 160.5 (s); 191.6 (s); MS *m/z* 320 (M^+, 0.1), 262 (16); 247 (100); anal $C_{17}H_{20}O_4S$ (C, H, N, S).

2,2-Dimethyl-5-(4-nitroanilinomethylidene)-1,3-dioxane-4,6-dione ***6a***. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (8.8 g, 61.0 mmol) and trimethyl orthoformate (300 mL) were refluxed for 2 h. Then a solution of 4-nitroaniline (5.0 g, 36.6 mmol) in trimethyl orthoformate (300 mL) was added and the reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel. Elution with hexane/dichloromethane (70:30) gave **6a** (9.6 g, 90%) as an orange solid; mp = 215–217 °C (from dichloromethane/methanol); IR (KBr): 1733, 1679, 1515, 1236 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.80 (s, 6H); 7.46 (d, *J* = 9.1 Hz, 2H); 8.37 (d, *J* = 9.1 Hz, 2H); 8.78 (s, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD 50 MHz) δ: 26.88 (q); 89.37 (s); 105.64 (s); 117.86 (2d); 125.80 (2d); 142.80 (s); 145.25 (s); 151.84 (d); 163.29 (s); 164.99 (s); MS *m/z* 293 (M +1, 3); 292 (M^+, 20); 277 (1); 234 (100); anal $C_{13}H_{12}N_2O_6$•0.25 H_2O (C, H, N).

2,2-Dimethyl-5-(3-nitroanilinomethylidene)-1,3-dioxane-4,6-dione ***6b***. 2,2-Dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) (8.8 g, 61.0 mmol) and trimethyl orthoformate (300 mL) were refluxed for 2 h. Then a solution of 3-nitroaniline (5.0 g, 36.6 mmol) in trimethyl orthoformate (300 mL) was added and the reaction mixture was refluxed for 3 h. The solvent was evaporated under reduced pressure and the residue was purified by flash column chromatography on silica gel. Elution with hexane/dichloromethane (70:30) gave **6b** (9.5 g, 90%) as an orange solid; mp = 215–217 °C (from dichloromethane/methanol); IR (KBr): 3231, 1726, 1676, 1527, 1272 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.78 (s, 6H); 7.50–7.71 (m, 2H); 8.10–8.20 (m, 2H); 8.71 (d, *J* = 13.9 Hz, 1H); 11.40 (d, *J* = 13.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 26.9 (q); 105.6 (s); 112.9 (d); 121.0 (d); 123.6 (d); 131.1 (d); 138.9 (s); 149.1 (s); 152.3 (d); 163.4 (s); 165.1 (s); MS *m/z* 292 (M^+, 2); 291 (11); 232 (55); 115 (88); 114 (100); anal $C_{13}H_{12}N_2O_6$ (C, H, N).

2,2-Dimethyl-5-[1-(3-nitroanilino)ethylidene]-1,3-dioxane-4,6-dione ***6c***. A solution of **5b** [25] (10 g, 46.3 mmol) and 3-nitroaniline (6.4 g, 46.3 mmol) in ethanol (120 mL) was refluxed for 3 h under nitrogen. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography. Elution with dichloromethane gave **6c** (10.77 g, 76%); mp = 143–144 °C (from dichloromethane); IR (KBr): 1708, 1659, 1532, 1357 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.75 (s, 6H); 2.63 (s, 3H); 7.59 (dd, *J* = 8.0 and 2.2 Hz, 1H); 7.71 (dd, *J* = 8.2 and 8.0 Hz, 1H); 8.12 (dd, *J* = 2.2 and 2.0 Hz, 1H); 8.27 (dd, *J* = 8.2 and 2.0 Hz, 1H); 12.52 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 19.7 (q); 26.5 (2q); 86.9 (s); 103.0 (s); 121.2 (d); 122.8 (d); 130.6 (d); 132.0 (d); 137.2 (s); 144.2 (s); 162.3 (s); 167.3 (s); 172.9 (s); MS *m/z* 307 (M+1, 1); 306 (M^+, 4); 249 (26); 248 (100); anal $C_{14}H_{14}N_2O_6$ (C, H, N).

Methyl 4-bromomethyl-3-methoxybenzoate ***7a***. A solution of methyl 4-methyl-3-methoxybenzoate (3 g, 17.1 mmol), *N*-bromosuccinimide (3.26 g, 18.5 mmol) and 2,2'-azobisisobutyronitrile (1 mg) in carbon tetrachloride (132 mL) was refluxed for 4 h. The reaction mixture was filtered and the solution was washed with brine, dried over Na_2SO_4 and evaporated to give **7a** (4.4 g, 97%); mp = 73–75 °C (from ether); IR (KBr): 1717, 758 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.92 (s, 3H); 3.96 (s, 3H); 4.55 (s, 2H); 7.39 (d, *J* = 7.8 Hz, 1H); 7.54 (d, *J* = 1.6 Hz, 1H); 7.61 (dd, *J* = 7.8 and 1.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 27.9 (t); 52.5 (q); 56.0 (q); 111.9 (d); 122.3 (d); 130.5 (s); 130.9 (d); 131.3 (s); 157.4 (s); 166.8 (s); MS *m/z* 260 (M+1, 5); 259 (M^+, 12); 229 (5); 179 (100); anal $C_{10}H_{11}O_3Br$ (C, H).

Methyl 4-hydroxymethyl-3-methoxybenzoate ***7c***. A mixture of **7a** (904 mg, 3.5 mmol) and Amberlite carbonate (5.5 g, 12.8 meq) in benzene (12 mL) was refluxed for 45 min. The reaction mixture was filtered and the solid residue was washed with methanol. The collected organic layer was evaporated and the residue was purified by flash column chromatography. Elution with dichloromethane afforded **7c** (343 mg, 50%); mp = 84–86 °C (from diisopropyl ether/acetone); IR (KBr): 3321, 1713, 1294, 1265 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.87 (s, 3H); 3.90 (s, 3H); 4.70 (s, 2H); 7.37 (d, *J* = 7.8 Hz, 1H); 7.48 (d, *J* = 1.4 Hz, 1H); 7.60 (d, *J* = 7.8 and 1.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.7 (q); 56.0 (q); 61.7 (t); 111.2 (d); 122.7 (d); 128.3 (d); 130.9 (s); 134.9 (s); 157.4 (s); 167.5 (s); MS *m/z* 196 (M^+, 100); 165 (64); 137 (92); anal $C_{10}H_{12}O_4$ (C, H, N).

Methyl 4-formyl-3-methoxybenzoate ***7d***. A mixture of **7c** (1.8 g, 9.2 mmol) and MnO_2 (6.9 g, 79.4 mmol) in dichloromethane (287 mL) was refluxed for 15 h. The mixture was filtered over Celite and the solvent evaporated to give **7d** (1.4 g, 78%); mp = 78–81 °C (from diisopropyl ether); IR (KBr): 1726, 1685, 1295 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.85 (s, 3H); 3.89 (s, 3H); 7.30–7.60 (m, 2H); 7.74 (d, *J* = 8.3 Hz, 1H); 10.39 (s, 1 H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.5 (q); 55.8 (q); 112.6 (d); 121.4 (d); 127.5 (s); 128.2 (d); 136.2 (s); 161.2 (s); 165.8 (s); 189.1 (d); MS *m/z* 196 (M+2, 2); 195 (M+1, 13); 194 (M^+, 100); 163 (75); 135 (67); 119 (34); anal $C_{10}H_{10}O_4$ (C, H, N).

General procedure for preparation of ***8a, 8b***

A solution of the corresponding 4-quinolone **2l** or **2n** (1 mmol) in tetrahydrofuran (40 mL) was added very slowly to a stirred solution of lithium diisopropylamide (3 mmol) in tetrahydrofuran (15 mL) cooled at –78 °C. The mixture was stirred under nitrogen for a further 30 min at –78 °C. A solution of **7d** (2 mmol) in tetrahydrofuran (10 mL) was added, the reaction mixture was stirred for 30 min at –78 °C and then for 2 h at room temperature. Aqueous ammonium chloride was added and the organic solvent removed under reduced pressure. The aqueous solution was extracted with dichloromethane, and the organic solution dried over Na_2SO_4 and evaporated. The product was purified by flash column chromatography with ethyl acetate/methanol (90:10) as eluent.

2-(1-Hydroxy-2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-6-nitro-4-oxo-1,4-dihydroquinoline ***8a***. Yield 30%; mp = 218–220 °C (from dichloromethane/methanol); IR (KBr): 3266, 1731, 1635, 1492 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 3.81 (s, 3H); 3.89 (s, 3H); 3.94 (s, 3H); 6.26 (s, 1H); 6.48 (s, 1H); 7.48 (d, *J* = 7.9 Hz, 1H); 7.59 (d, *J* = 1.5 Hz, 1H); 7.64 (d, *J* = 9.5 Hz, 1H); 7.69 (dd, *J* = 7.9 and 1.5 Hz, 1H); 8.41 (dd, *J* = 9.5 and 2.8 Hz, 1H); 9.12 (d, *J* = 2.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 35.0 (q); 52.2 (q); 55.7 (q); 66.6 (d); 111.1 (d); 111.3 (d); 117.2 (d); 122.3 (d); 122.5 (d); 125.3 (s); 126.2 (d); 127.6 (d); 131.5 (s); 132.5 (s); 143.0 (s); 145.1 (s); 155.9 (s); 157.4 (s); 166.6 (s); 177.6 (s); MS *m/z* 400 (M+2, 1); 399 (M+1, 5); 398 (M^+, 16); 367 (21); 218 (100); anal $C_{20}H_{18}N_2O_7$ (C, H, N).

2-(1-Hydroxy-2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-7-nitro-4-oxo-1,4-dihydroquinoline ***8b***. Yield 30%; mp = 214–216 °C (from dichloromethane/methanol); IR (KBr): 3120, 1730, 1593, 1503 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.86 (s, 3H); 3.92 (s, 3H); 3.96 (s, 3H); 6.30 (s, 1H); 6.57 (s, 1H); 7.49 (d, *J* = 7.9 Hz, 1H); 7.62 (s, 1H); 7.72 (d, *J* = 7.9 Hz, 1H); 8.17 (dd, *J* = 8.8 and 1.6 Hz, 1H); 8.49 (d, *J* = 1.6 Hz, 1H); 8.56 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 32.5 (q); 49.5 (q); 53.4 (q); 64.4 (d); 108.8 (d); 109.1 (d); 109.7 (d); 115.0 (d); 120.1 (d); 125.3 (d); 126.1 (d); 126.9 (s); 129.2 (s); 130.1 (s); 139.4 (s); 147.5 (s); 153.6 (s); 155.5 (s); 164.3 (s); 175.1 (s); MS *m/z* 400 (M+2, 1); 399 (M+1, 2); 398 (M^+, 17); 367 (26); 218 (100); anal $C_{20}H_{18}N_2O_7$ (C, H, N).

General procedure for preparation of compounds ***8c, 8d***

Methanesulfonyl chloride (1.5 mmol) was added to a stirred solution of corresponding alcohol **8a** or **8b** (1 mmol) and triethylamine (1.8 mmol) in dichloromethane (15 mL) cooled at 0 °C under nitrogen. The reaction mixture was stirred for 1 h. The organic solution was washed with saturated aqueous sodium hydrogen carbonate (3 x 15 mL), dried over Na_2SO_4, and evaporated. The mesyl derivatives obtained were used in the following reaction without further purification.

2-(1-Mesyloxy-2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-6-nitro-4-oxo-1,4-dihydroquinoline ***8c***. Yield 90%; IR (NaCl): 1722, 1338, 1177 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.10 (s, 3H); 3.77 (s, 3H); 3.96 (s, 3H); 4.04 (s, 3H); 6.63 (s, 1H); 7.31 (s, 1H); 7.45 (d, *J* = 7.7 Hz, 1H); 7.64–7.74 (m, 3H); 8.46 (dd, *J* = 9.5 and 2.8 Hz, 1H); 9.21 (d, *J* = 2.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 35.2 (q); 39.4 (q); 52.6 (q); 56.3 (q); 72.3 (d); 112.2 (d); 112.6 (d); 117.2 (d); 122.7 (d); 123.1 (d); 126.2 (s); 126.6 (s); 126.7 (d); 128.6 (d); 133.5 (s); 143.5 (s); 145.3 (s); 150.9 (s); 156.0 (s); 166.9 (s); 176.7 (s).

2-(1-Mesyloxy-2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-7-nitro-4-oxo-1,4-dihydroquinoline ***8d***. Yield 96%; IR (NaCl): 1721, 1640, 1351, 1177 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.07 (s, 3H); 3.78 (s, 3H); 3.94 (s, 3H); 4.01 (s, 3H); 6.63 (s, 1H); 7.22 (s, 1H); 7.42 (d, *J* = 8.0 Hz, 1H); 7.68–7.71 (m, 2H); 8.17 (d, *J* = 8.7 Hz, 1H); 8.44 (d, *J* = 1.8 Hz, 1H); 8.57 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 35.1 (q); 39.3 (q); 52.4 (q); 56.2 (q); 72.1 (d); 111.9 (d); 112.1 (d); 112.3 (d); 117.9 (d); 121.8 (s); 122.5 (d); 126.5 (s); 128.5 (d); 128.6 (d); 129.3 (s); 133.4 (s); 141.9 (s); 150.0 (s); 150.9 (s); 155.9 (s); 165.7 (s); 176.0 (s).

General procedure for preparation of ***8e–o***

A solution of the corresponding nitroquinolone **2d–h**, **2j–k** (1 mmol) in dry tetrahydrofuran (5 mL) was added to a stirred suspension of oil-free sodium hydride (2 mmol) in dry tetrahydrofuran (5 mL). The mixture was stirred for 30 min at 0 °C under nitrogen. A solution of **7a** or **7b** (2 mmol) in dry tetrahydrofuran (3 mL) was added, and the mixture refluxed for 4 h. Saturated ammonium chloride aqueous solution (5 mL) was added, and the organic solvent removed under reduced pressure. The resulting aqueous solution was extracted with dichloromethane (3 x 5 mL). The organic layer was dried over Na_2SO_4 and evaporated to afford a residue which was purified by column chromatography.

1-(2-Methoxy-4-methoxycarbonylbenzyl)-6-nitro-4-oxo-1,4-dihydroquinoline ***8e***. Elution with dichloromethane/methanol (99:1) gave **8e** (3.16 g, 82%); mp = 210–212 °C (from dichloromethane); IR (KBr): 1721, 1645, 1486, 1336 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 3.88 (s, 3H); 3.96 (s, 3H); 5.34 (s, 2H); 6.40 (d, *J* = 8.0 Hz, 1H); 6.85 (d, *J* = 8.0 Hz, 1H); 7.37 (d, *J* = 9.5 Hz, 1H); 7.53 (dd, *J* = 8.0 and 1.5 Hz, 1H); 7.60 (d, *J* = 1.5 Hz, 1H); 7.68 (d, *J* = 8.0 Hz, 1H); 8.31 (dd, *J* = 9.5 and 2.5 Hz, 1H); 9.27 (d, *J* = 2.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.2 (t); 52.2 (q); 55.6 (q); 111.3 (d); 111.4 (d); 115.4 (d); 122.1 (d); 123.2 (d); 126.2 (d); 126.9 (s); 127.0 (d); 127.0 (s); 131.6 (s); 143.1 (s); 143.3 (s); 145.2 (d); 156.4 (s); 166.2 (s); 177.4 (s); MS *m/z* 369 (M+1, 3); 368 (M^+, 12); 179 (100); 151 (21); 149 (22); anal $C_{19}H_{16}N_2O_6$ (C, H, N).

1-(2-Methoxy-4-methoxycarbonylbenzyl)-5-nitro-4-oxo-1,4-dihydroquinoline ***8f*** *and 1-(2-methoxy-4-methoxycarbonylbenzyl)-7-nitro-4-oxo-1,4-dihydroquinoline* ***8g***. Elution with dichloromethane gave **8f** (760 mg, 47%); mp = 189–191 °C (from dichloromethane); IR (KBr): 1720, 1635, 1607, 1292 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.91 (s, 3H); 3.98 (s, 3H); 5.36 (s, 2H); 6.28 (d, *J* = 7.9 Hz, 1H); 6.85 (d, *J* = 7.9 Hz, 1H); 7.23 (dd, *J* = 7.9 and 1.0 Hz, 1H); 7.41 (dd, *J* = 7.9 and 1.0 Hz, 1H); 7.52–7.61 (m, 3H); 7.66 (d, *J* = 7.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.3 (q); 52.4 (t); 55.7 (q); 111.2 (d); 111.6 (d); 117.5 (d); 117.7 (s); 118.6 (d); 122.1 (d); 126.8 (d); 127.3 (2s); 131.6 (d); 140.8 (s); 144.1 (d); 149.3 (s); 156.4 (s); 166.2 (s); 174.4 (s); MS *m/z* 369 (M+1, 1); 368 (M^+, 4); 179 (100); 151 (29); 149 (31); anal $C_{19}H_{16}N_2O_6 \cdot 0.25\ H_2O$ (C, H, N). Elution with dichloromethane/methanol (99:1) gave **8g** (800 mg, 50%); mp = 138–140 °C (from dichloromethane); IR (KBr): 1721, 1638, 1599 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H); 4.05 (s, 3H); 5.40 (s, 2H); 6.42 (d, *J* = 7.8 Hz, 1H); 7.05 (d, *J* = 7.9 Hz, 1H); 7.58 (dd, *J* = 7.9 and 1.5 Hz, 1H); 7.60 (d, *J* = 1.5 Hz, 1H); 7.82 (d, *J* = 7.8 Hz, 1H); 8.10 (dd, *J* = 8.8 and 1.9 Hz, 1H); 8.39 (d, *J* = 1.9 Hz, 1H); 8.58 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.0 (t); 52.7 (q); 56.2 (q); 112.0 (2d); 112.7 (d); 117.7 (d); 122.6 (d); 127.2 (s); 128.0 (d); 129.4 (d); 130.7 (s); 132.4 (s); 140.2 (s); 145.5 (d); 150.0 (s); 156.9 (s); 177.2 (s); MS *m/z* 369 (M+1, 1); 368 (M^+, 5); 338 (6); 179 (100); 151 (28); anal $C_{19}H_{16}N_2O_6 \cdot H_2O$ (C, H, N).

1-(2-Methoxy-4-methoxycarbonylbenzyl)-2-methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***8h*** *and 1-(2-methoxy-4-methoxycarbonylbenzyl)-2-methyl-7-nitro-4-oxo-1,4-dihydroquinoline* ***8i***. Elution with dichloromethane gave **8i**; yield 22%; mp = 142–144 °C (from dichloromethane); IR (KBr): 1735, 1730, 1536, 1343 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.73 (s, 3H); 3.95 (s, 3H); 3.97(s, 3H); 5.38 (s, 2H); 6.85 (s, 1H); 7.58 (d, *J* = 7.8 Hz, 1H); 7.63 (d, *J* = 1.4 Hz, 1H); 7.72 (dd, *J* = 7.8 and 1.4 Hz, 1H); 8.21 (dd, *J* = 9.2 and 2.0 Hz, 1H); 8.36 (d, *J* = 9.2 Hz, 1H); 8.85 (d, *J* = 2.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 26.0 (q); 52.4 (q); 55.7 (q); 65.4 (t); 104.2 (d); 111.2 (d); 118.3 (d); 122.2 (d); 123.5 (s); 123.7 (d); 124.3 (d); 127.8 (d); 128.6 (s); 131.2 (s); 148.0 (s); 148.6 (s); 156.6 (s); 160.9 (s); 163.0 (s); 166.7 (s); MS *m/z* 383 (M+1, 1); 382 (M^+, 1); 351 (3); 179 (100); anal $C_{20}H_{18}N_2O_6 \cdot 0.25\ H_2O$ (C, H, N). Elution with dichloromethane/methanol (99:1) gave **8h**; yield 19%; mp = 154–156 °C (from dichloromethane/methanol); IR (KBr): 1718, 1601, 1536, 1384 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.74 (s, 3H); 3.92 (s, 3H); 3.95 (s, 3H); 5.33 (s, 2H); 6.87 (s, 1H); 7.44–7.66 (m, 5H); 8.21 (dd, *J* = 8.8 and 1.0 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 24.2 (q); 51.7 (q); 54.7 (q); 65.1 (t); 103.3 (d), 109.9 (d), 118.9 (d); 121.4 (d); 121.5 (s); 126.7 (d); 126.9 (d); 127.8 (d); 129.2 (s); 129.8 (d); 130.2 (s); 147.6 (s); 155.2 (s); 158.7 (s); 160.9 (s); 165.7 (s); MS *m/z* 382 (M^+, 1); 351 (3); 179 (100); anal $C_{20}H_{18}N_2O_6 \cdot 0.25\ H_2O$ (C, H, N).

1-(4-Methoxycarbonylbenzyl)-2-methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***8j*** *and 1-(4-methoxycarbonyl-benzyl)-2-methyl-7-nitro-4-oxo-1,4-dihydroquinoline* ***8k***. Elution with dichloromethane gave **8k** (28%); mp = 144–146 °C (from dichloromethane); IR (KBr): 1722, 1601, 1533, 1345 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.73 (s, 3H); 3.95 (s, 3H); 5.38 (s, 2H); 6.83 (s, 1H); 7.59 (d, *J* = 8.0 Hz, 2H); 8.14 (d, *J* = 8.0 Hz, 2H); 8.20 (dd, *J* = 9.1 and 2.2 Hz, 1H); 8.34 (d, *J* = 9.1 Hz, 1H); 8.83 (d, *J* = 2.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 26.0 (q); 52.3 (q); 69.9 (t); 104.1 (d); 118.3 (d); 123.3 (s); 123.6 (d); 124.3 (d); 127.1 (2d); 130.1 (2d); 130.4 (s); 134.0 (s); 147.9 (s); 148.5 (s); 160.6 (s); 162.9 (s); 166.5 (s); MS *m/z* 353 (M+1, 3); 352 (M^+, 11); 149 (100); anal $C_{19}H_{16}N_2O_5 \cdot 0.5\ H_2O$ (C, H, N). The subsequent fractions gave **8j** (14%); mp = 140–142 °C (from dichloromethane/methanol); IR (KBr): 1720, 1597, 1539, 1373 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.62 (s, 3H); 3.85 (s, 3H); 5.23 (s, 2H); 6.71 (s, 1H); 7.40–7.47 (m, 3H); 7.62 (dd, *J* = 8.4 and 7.6 Hz, 1H); 8.00–8.09 (m, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 25.6 (q); 52.1 (q); 70.3 (t); 104.1 (d); 119.7 (d); 126.5 (2d); 130.0 (2d); 130.1 (s); 131.3 (d); 139.4 (s); 129.8 (d); 130.2 (s); 147.3 (s); 149.8 (s); 159.0 (s); 161.8 (s); 166.2 (s); MS *m/z* 353 (M+1, 1); 352 (M^+, 3); 149 (100); anal $C_{19}H_{16}N_2O_5 \cdot 0.5\ H_2O$ (C, H, N).

1-(2-Methoxy-4-methoxycarbonylbenzyl)-3-methyl-5-nitro-4-oxo-1,4-dihydroquinoline ***8l*** *and 1-(2-methoxy-4-methoxycar-*

bonylbenzyl)-3-methyl-7-nitro-4-oxo-1,4-dihydroquinoline ***8m***. Elution with ethyl acetate gave **8l** (50%); mp = 202–204 °C (from dichloromethane/methanol); IR (KBr): 1711, 1637, 1589, 1496 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.99 (s, 3H); 3.83 (s, 3H); 3.91 (s, 3H); 5.28 (s, 2H); 6.68 (d, *J* = 8.2 Hz, 1H); 7.12 (d, *J* = 6.6 Hz, 1H); 7.28 (d, *J* = 8.0 Hz, 1H); 7.40–7.56 (m, 4H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 13.4 (q), 52.1 (t); 52.3 (q); 55.7 (q); 111.2 (d); 117.2 (d); 118.2 (d); 121.8 (s); 122.2 (d); 126.6 (d); 127.1 (s); 131.2 (d); 131.6 (s); 140.4 (s); 141.6 (d); 149.5 (s); 156.7 (s); 166.2 (s); 174.7 (s); MS *m/z* 383 (M+1, 3); 382 (M^+, 13); 179 (100); 149 (20); anal $C_{20}H_{18}N_2O_6$• 1.5 CH_2Cl_2 (C, H, N). The subsequent fractions gave **8m** (39%); mp = 198–200 °C (from dichloromethane); IR (KBr): 1719; 1640; 1594; 1347 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.19 (s, 3H); 3.90 (s, 3H); 4.05 (s, 3H); 5.39 (s, 2H); 6.96 (d, *J* = 7.8 Hz, 1H); 7.75 (dd, *J* = 7.8 and 1.4 Hz, 1H); 6.63 (d, *J* = 1.4 Hz, 1H); 7.78 (s, 1H); 8.05 (dd, *J* = 8.8 and 1.8 Hz, 1H); 8.32 (d, *J* = 1.8 Hz, 1H); 8.60 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 13.8 (q); 51.3 (t); 52.3 (q); 55.9 (q); 111.5 (d); 112.1 (d); 116.7 (d); 120.7 (s); 122.2 (d); 127.3 (d); 128.5 (s); 129.1 (d); 131.9 (s); 139.7 (s); 142.7 (d); 149.4 (s); 142.7 (d); 149.4 (s); 156.4 (s); 165.3 (s); 177.8 (s); MS *m/z* 383 (M+1, 3); 382 (M^+, 11); 179 (100); anal $C_{20}H_{18}N_2O_6$•H_2O (C, H, N).

1-(4-Methoxycarbonylbenzyl)-5-nitro-4-oxo-1,4-dihydroquinoline ***8n*** *and 1-(4-methoxycarbonylbenzyl)-7-nitro-4-oxo-1,4-dihydroquinoline* ***8o***. Elution with ethyl acetate gave **8n** (31%); mp = 201–203 °C (from dichloromethane); IR (KBr): 1717, 1606, 1542, 1359 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.93 (s, 3H); 5.44 (s, 2H); 6.32 (d, *J* = 7.8 Hz, 1H); 7.21(d, *J* = 8.5 Hz, 2H); 7.26 (dd, *J* = 7.6 and 0.8 Hz, 1H); 7.36 (dd, *J* = 7.6 and 0.8 Hz, 1H); 7.56 (dd, *J* = 7.6 and 7.6 Hz, 1H); 7.68 (d, *J* = 7.8 Hz, 1H); 8.05 (d, *J* = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.3 (q); 56.9 (t); 112.2 (d); 117.8 (d); 118.6 (d); 125.8 (2d); 130.7 (2d); 131.8 (d); 139.2 (s); 143.8 (d); MS *m/z* 339 (M+1, 4); 338 (M^+, 19); 149 (100); anal $C_{18}H_{14}N_2O_5$•0.5 H_2O (C, H, N). The subsequent fractions gave **8o** (18%) mp = 173–175 °C (from dichloromethane); IR (KBr): 1718, 1601, 1572, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H); 5.45 (s, 2H); 6.46 (d, *J* = 7.6 Hz, 1H); 7.27 (d, *J* = 8.5 Hz, 2H); 7.78 (d, *J* = 7.6 Hz, 1H); 8.05 (d, *J* = 8.5 Hz, 2H); 8.11 (dd, *J* = 8.8 and 1.8 Hz, 1H); 8.18 (d, *J* = 1.8 Hz, 1H); 8.60 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.3 (q); 56.6 (t); 112.1 (d); 117.7 (d); 126.1 (2d); 129.4 (d); 130.4 (s); 130.8 (2d); 138.9 (s); 140.0 (s); 144.9 (d); 149.1 (s); 166.2 (s); 176.3 (s); MS *m/z* 339 (M+1, 7); 338 (M^+, 28); 149 (100); anal $C_{18}H_{14}N_2O_5$•H_2O (C, H, N).

General procedure for preparation of compounds ***9a, 9b***
Sodium borohydride (6 mmol) was added to a stirred solution of the corresponding mesyl derivative **8c** or **8d** (1 mmol) in isopropanol (15 mL), and the mixture stirred for 3 h. The solvent was evaporated and the residue dissolved in water and extracted with dicholoromethane. The organic solution was dried over Na_2SO_4 and evaporated. The product was purified by flash column chromatography with dichloromethane/methanol (99:1) as eluent.

2-(2-Methoxy-4-methoxycarbonylbenzyl)-1-methyl-6-nitro-4-oxo-1,4-dihydroquinoline ***9a***. Yield 31%; mp = 230–232 °C (from dichloromethane/methanol); IR (KBr): 1634, 1609, 1488, 1337, 1291 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 3.67 (s, 3H); 3.92 (s, 3H); 3.95 (s, 3H); 4.13 (s, 2H); 6.20 (s, 1H); 7.07 (d, *J* = 8.2 Hz, 1H); 7.56–7.62 (m, 3H); 8.40 (dd, *J* = 9.4 and 2.8 Hz, 1H); 9.20 (d, *J* = 2.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 34.5 (t); 35.0 (q); 52.3 (q); 55.8 (q); 111.4 (d); 114.3 (d); 116.8 (d); 122.6 (d); 123.2 (d); 126.1 (s); 126.2 (d); 128.7 (s); 129.2 (d); 130.9 (s); 143.1 (s); 145.3 (s); 153.6 (s); 156.5 (s); 166.5 (s); 176.7 (s); MS *m/z* 384 (M+2, 2); 383 (M+1, 10); 382 (M^+, 36); 351 (49); 218 (100); anal $C_{20}H_{18}N_2O_6$•0.5 H_2O (C, H, N).

2-(2-Methoxy-4-methoxycarbonylbenzyl)-1-methyl-7-nitro-4-oxo-1,4-dihydroquinoline ***9b***. Yield 63%; mp = 227–229 °C (from dichloromethane/methanol); IR (NaCl): 1720, 1632, 1600, 1463, 1291 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.71 (s, 3H); 3.93 (s, 3H); 3.95 (s, 3H); 4.15 (s, 2H); 6.31 (s, 1H); 7.06 (d, *J* = 8.2 Hz, 1H); 7.57–7.61 (m, 2H); 8.17 (dd, *J* = 8.8 and 1.8 Hz, 1H); 8.43 (d, *J* = 1.8 Hz, 1H); 8.61 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 34.4 (t); 34.6 (q); 52.1 (q); 55.5 (q); 96.7 (d); 111.0 (d); 111.2 (d); 111.9 (d); 119.8 (s); 122.2 (d); 126.8 (d); 128.7 (d); 129.6 (s); 130.2 (s); 143.7 (s); 152.3 (s); 154.9 (s); 156.3 (s); 166.8 (s); 177.5 (s); MS *m/z* 383 (M+1, 4); 382 (M^+, 15); 351 (24); 218 (100); anal $C_{20}H_{18}N_2O_6$• 2 MeOH (C, H, N).

General procedure for reduction using catalytic hydrogenation. Preparation of compounds ***10a,b, 10f, h***
Pd-C (10% w/w) was added to a solution of the corresponding nitrocompound **9a,b**, **8i** or **8m** (1 mmol) in methanol (5 mL) and trifluoroacetic acid (0.5 mL), and the mixture was hydrogenated at atmospheric pressure for 20 h. The mixture was filtered over Celite and the solvent was evaporated. The residue was dissolved in saturated sodium hydrogen carbonate solution (5 mL), and the aqueous layer was extracted with dichloromethane (2 x 5 mL). The combined extracts were dried and evaporated. The product was purified by chromatography using ethyl acetate as eluent.

6-Amino-2-(2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline ***10a***. Yield 91%; mp = 198–200 °C (from dichloromethane); IR (NaCl): 3385, 1701, 1594 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.52 (s, 3H); 3.90 (s, 3H); 3.93 (s, 3H); 4.05 (s, 2H); 6.15 (s, 1H); 7.00 (d, *J* = 8.0 Hz, 1H); 7.05 (dd, *J* = 8.5 and 2.2 Hz, 1H); 7.30 (d, *J* = 8.5 Hz, 1H); 7.50–7.60 (m, 2H); 7.67 (d, *J* = 2.2 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 34.3 (t); 34.4 (q); 52.2 (q); 55.6 (q); 109.0 (d); 111.0 (d); 111.6 (d); 116.7 (d); 121.3 (d); 122.2 (d); 127.8 (s); 128.9 (d); 129.7 (s); 130.3 (s); 135.2 (s); 142.9 (s); 150.6 (s); 156.3 (s); 166.6 (s); 177.1 (s); MS *m/z* 353 (M+1, 24); 352 (M^+, 100); 322 (12); 188 (94); anal $C_{20}H_{20}N_2O_4$ (C, H, N).

7-Amino-2-(2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline ***10b***. Yield 71%; mp = 240–242 °C (from dichloromethane); IR (NaCl): 3343, 1718, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.41 (s, 3H); 3.91 (s, 3H); 3.92 (s, 3H); 4.01 (s, 2H); 6.10 (s, 1H); 6.52 (s, 1H); 6.67 (d, *J* = 8.4 Hz, 1H); 6.96 (d, *J* = 7.8, 1H); 7.48–7.54 (m, 2H); 8.16 (d, *J* = 8.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 34.3 (t); 34.4 (q); 52.2 (q); 55.6 (q); 97.5 (d); 111.0 (d); 112.3 (d); 112.8 (d); 118.7 (s); 122.2 (d); 128.2 (d); 128.9 (d); 129.9 (s); 130.3 (s); 144.0 (s); 150.7 (s); 151.0 (s); 156.3 (s); 166.7 (s); 177.1 (s); MS *m/z* 353 (M+1, 2); 352 (M^+, 4); 188 (13); 129 (11); anal $C_{20}H_{20}N_2O_4$ (C, H, N).

7-Amino-1-(2-methoxy-4-methoxycarbonylbenzyl)-2-methyl-4-oxo-1,4-dihydroquinoline ***10f***. Yield 75%; mp = 148–150 °C (from dichloromethane/methanol); IR (KBr): 3412, 1716, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 2.66 (s, 3H); 3.94 (s, 3H); 3.95 (s, 3H); 5.32 (s, 2H); 6.50 (s, 1H); 6.89 (dd, *J* = 8.8 and 1.8 Hz, 1H); 7.20 (d, *J* = 1.8 Hz, 1H); 7.56–7.60 (m,

2H); 7.70 (dd, J = 8.2 and 1.5 Hz, 1H); 8.02 (d, J = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 24.4 (q); 52.0 (q); 55.3 (q); 64.7 (t); 99.7 (d); 106.4 (d); 110.6 (d); 114.2 (s); 114.2 (d); 121.9 (d); 122.2 (d); 127.2 (d); 129.3 (s); 130.5 (s); 149.0 (s); 152.9 (s); 156.1 (s); 159.9 (s); 161.6 (s); 166.9 (s); MS *m/z* 353 (M+1, 13); 352 (M^+, 56); 321 (4); 179 (100); anal $C_{20}H_{20}N_2O_4 \cdot H_2O$ (C, H, N).

7-Amino-1-(2-methoxy-4-methoxycarbonylbenzyl)-3-methyl-4-oxo-1,4-dihydroquinoline ***10h***. Yield 89%; mp = 126–128 °C (from dichloromethane/methanol); IR (KBr): 1722, 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.10 (s, 3H); 3.90 (s, 3H); 3.99 (s, 3H); 5.28 (s, 2H); 6.22 (d, J = 1.9 Hz, 1H); 6.62 (dd, J = 8.8 and 1.9 Hz, 1H); 6.66 (d, J = 8.7 Hz, 1H); 7.41 (s, 1H); 7.45 (dd, J = 8.7 and 1.4 Hz, 1H); 7.58 (d, J = 1.4 Hz, 1H); 8.27 (d, J = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 13.8 (q); 51.4 (t); 52.3 (q); 55.7 (q); 97.2 (d); 110.9 (d); 113.2 (d); 118.1 (s); 118.3 (s); 122.3 (d); 126.5 (d); 128.7 (d); 130.9 (s); 140.7 (d); 142.0 (s); 150.0 (s); 156.2 (s); 166.6 (s); 177.4 (s); MS *m/z* 353 (M+1, 27); 352 (M^+, 100); 293 (4); 179 (84); 173 (86); anal $C_{20}H_{20}N_2O_4 \cdot CH_2Cl_2$ (C, H, N).

General procedure for reduction using NH_4HCO_2, Pd/C. Preparation of ***10c–e***

Ammonium formate (8 mmol) was added to a suspension of the corresponding nitroquinolone **8e–g** (1 mmol) and Pd-C (10% w/w) in methanol (25 mL) under nitrogen. The mixture was refluxed for 2.5 h. The cooled mixture was filtered over Celite and the solvent was evaporated. The residue was partitioned between dichloromethane (20 mL) and saturated sodium hydrogen carbonate solution (20 mL), and the aqueous layer was extracted with dichloromethane (2 x 20 mL). The combined extracts were dried over Na_2SO_4 and evaporated.

6-Amino-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***10c***. Yield 97%; mp = 217–219 °C (from dichloromethane); IR (KBr): 3426, 3330, 1720, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H); 3.98 (s, 3H); 5.28 (s, 2H); 6.26 (d, J = 7.6 Hz, 1H); 6.75 (d, J = 7.9 Hz, 1H); 6.92 (dd, J = 9.0 and 2.8 Hz, 1H); 7.06 (d, J = 9.0 Hz, 1H); 7.49 (dd, J = 7.9 and 1.3 Hz, 1H); 7.53 (d, J = 7.6 Hz, 1H); 7.59 (d, J = 1.3 Hz, 1H); 7.69 (d, J = 2.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 51.6 (t); 52.1 (q); 55.5 (q); 108.1 (d); 108.3 (d); 110.8 (d); 117.2 (d); 121.7 (d); 122.0 (d); 126.6 (d); 128.1 (s); 128.4 (s); 130.9 (s); 132.8 (s); 142.6 (d); 143.7 (s); 156.1 (s); 166.4 (s); 177.8 (s); MS *m/z* 339 (M+1, 24); 338 (M^+, 100); 179 (93); 151 (29); 149 (28); anal $C_{19}H_{18}N_2O_4$ (C, H, N).

5-Amino-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***10d***. Yield 98%; mp = 151–154 °C (from dichloromethane); IR (KBr): 3450, 1717, 1631 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H); 3.96 (s, 3H); 5.16 (s, 2H); 6.14 (d, J = 7.6 Hz, 1H); 6.24 (d, J = 8.2 Hz, 1H); 6.34 (d, J = 8.2 Hz, 1H); 6.80 (d, J = 7.8 Hz, 1H); 7.14 (dd, J = 8.2 and 8.2 Hz, 1H); 7.24 (d, J = 7.6 Hz, 1H); 7.51 (dd, J = 7.8 and 1.4 Hz, 1H); 7.56 (d, J = 1.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.1 (t); 52.1 (q); 55.5 (q); 101.5 (d); 108.1 (d); 110.3 (d); 110.8 (d); 112.9 (s); 122.0 (d); 126.5 (d); 128.5 (s); 130.7 (s); 132.7 (d); 142.2 (s); 142.6 (d); 151.3 (s); 156.2 (s); 166.4 (s); 181.9 (s); MS *m/z* 339 (M+1, 25); 338 (M^+, 100); 179 (87); 151 (27); 149 (25); anal $C_{19}H_{18}N_2O_4$ (C, H, N).

7-Amino-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***10e***. Yield 92%; mp = 216–220 °C (from dichloromethane/methanol); IR (KBr): 3500, 1722, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.90 (s, 3H); 3.97 (s, 3H); 5.17 (s, 2H); 6.19 (d, J = 7.7 Hz, 1H); 6.26 (d, J = 1.9 Hz, 1H); 6.65 (dd, J = 8.7 and 1.9 Hz, 1H); 6.77 (d, J = 7.8 Hz, 1H); 7.43 (d, J = 7.7 Hz, 1H); 7.51 (dd, J = 7.8 and 1.4 Hz, 1H); 7.58 (d, J = 1.4 Hz, 1H); 8.22 (d, J = 8.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 51.6 (t); 52.3 (q); 55.7 (q); 97.6 (d); 109.9 (d); 110.8 (d); 111.2 (s); 113.3 (d); 122.3 (d); 126.7 (d); 128.5 (s); 128.6 (d); 131.0 (s); 142.2 (s); 143.0 (d); 150.6 (s); 156.3 (s); 166.5 (s); 177.7 (s); MS *m/z* 339 (M+1, 16); 338 (M^+, 58); 179 (100); anal $C_{19}H_{18}N_2O_4 \cdot 3$ MeOH (C, H, N).

General procedure for reduction using stannous chloride. Preparation of compounds ***10g***, ***10i***

Stannous chloride dihydrate (5 mmol) was added to a suspension of the corresponding nitroquinolone **8k** or **8o** (1 mmol) in ethanol (10 mL) under nitrogen. The mixture was refluxed for 3 h, evaporated and the residue partitioned between dichloromethane (25 mL) and saturated aqueous sodium bicarbonate (25 mL). The aqueous layer was extracted with dichloromethane (2 x 25 mL) and the extracts were dried over Na_2SO_4 and evaporated.

7-Amino-1-(4-methoxycarbonylbenzyl)-2-methyl-4-oxo-1,4-dihydroquinoline ***10g***. Yield 80%; mp = 186–188 °C (from dichloromethane); IR (NaCl): 3343, 3213, 1719, 1622 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.64 (s, 3H); 3.94 (s, 3H); 5.30 (s, 2H); 6.46 (s, 1H); 6.88 (d, J = 8.7 Hz, 1H); 7.17 (s, 1H); 7.55 (d, J = 8.0 Hz, 2H); 7.99 (d, J = 8.7 Hz, 1H); 8.10 (d, J = 8.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 25.2 (q); 52.1 (q); 69.2 (t); 99.0 (d); 107.8 (d), 112.6 (s), 116.6 (d), 118.8 (s); 122.9 (d); 126.8 (2d); 129.9 (2d); 140.9 (s); 148.5 (s); 150.0 (s); 160.0 (s); 161.0 (s); 166.6 (s); MS *m/z* 323 (M+1, 23); 322 (M^+, 80); 174 (27); 149 (100); anal $C_{19}H_{18}N_2O_3 \cdot CH_2Cl_2$ (C, H, N).

7-Amino-1-(4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***10i***. Yield 82%; mp = 148–150 °C (from dichloromethane/methanol); IR (KBr): 3350, 3222, 1719, 1616 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 3.85 (s, 3H); 5.26 (s, 2H); 6.22 (d, J = 7.6 Hz, 1H); 6.25 (d, J = 1.8 Hz, 1H); 6.65 (dd, J = 9.4 and 1.8 Hz, 1H); 7.14 (d, J = 8.6 Hz, 2H); 7.56 (d, J = 7.6 Hz, 1H); 7.94 (d, J = 8.6 Hz, 2H); 8.10 (d, J = 9.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 52.1 (t); 56.2 (q); 97.3 (d); 108.9 (d); 111.7 (s); 114.0 (d); 118.4 (s); 125.8 (2d); 128.3 (d); 130.3 (2d); 140.2 (s); 142.0 (s); 143.5 (d);151.8 (s); 166.1 (s); 176.9 (s); MS *m/z* 309 (M+1, 20); 308 (M^+, 77); 149 (100); anal $C_{18}H_{16}N_2O_3$ (C, H, N).

General procedure for preparation of compounds ***11a,b***, ***11f–j***

Cyclopentyl chloroformate (2 mmol) was added to a stirred solution of anilinoquinolone **10a,b** or **10e–i** (1 mmol) and *N*-methylmorpholine (2 mmol), in dichloromethane (5 mL) under nitrogen. The mixture was stirred for 2 h, poured into 1 N hydrochloric acid (3 mL), and extracted with dichloromethane (2 x 5 mL). The combined extracts were washed with brine (5 mL), dried, and evaporated to give a viscous oil. The product was purified by column chromatography.

6-Cyclopentyloxycarbonylamino-2-(2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline ***11a***. Yield (65%); mp = 163–165 °C (from dichloromethane); IR (KBr): 3460, 1721, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.50–1.90 (m, 8H); 3.75 (s, 3H); 3.91 (s, 3H); 3.94 (s, 3H); 4.20 (s, 2H); 5.10 (m, 1H); 6.65 (s, 1H); 7.01 (d, J = 7.8 Hz, 1H); 7.52–7.59 (m, 3H); 7.74 (brs, 1H); 8.13 (d, J = 2.2 Hz, 1H);

8.30 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 23.7 (2t); 32.6 (2t); 34.7 (t); 35.4 (q); 52.3 (q); 55.8 (q); 78.4.(d); 111.3 (2d); 113.5 (d); 116.9 (d); 122.4 (d); 124.9 (d); 125.5 (s); 129.1 (d); 130.7 (s); 135.8 (s); 137.6 (s); 153.4 (s); 153.7 (s); 156.4 (s); 166.5 (s); 174.9 (s); MS *m/z* 464 (M^+, 2); 378 (56); 214 (100); anal $C_{26}H_{28}N_2O_6$ (C, H, N).

7-Cyclopentyloxycarbonylamino-2-(2-methoxy-4-methoxycarbonylbenzyl)-1-methyl-4-oxo-1,4-dihydroquinoline ***11b***. Yield (70%); mp = 256–258 °C (from dichloromethane); IR (KBr): 3412, 1737, 1710, 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.60–1.90 (m, 8H); 3.64 (s, 3H); 3.93 (s, 3H); 3.97 (s, 3H); 4.16 (s, 2H); 5.20 (m, 1H); 6.24 (s, 1H); 7.01 (d, *J* = 7.6 Hz, 1H); 7.06 (dd, *J* = 8.8 and 1.8 Hz, 1H); 7.46–7.52 (m, 2H); 8.15 (m, 2H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 24.2 (2t); 33.4 (2t); 35.3 (t); 35.5 (q); 52.9 (q); 56.3 (q); 79.0 (d); 103.9 (d); 111.9 (d); 112.8 (d); 116.2 (d); 121.9 (s); 123.0 (d); 127.6 (d); 129.6 (d); 130.3 (s); 131.1 (s); 144.0 (s); 154.0 (s); 154.8 (s); 157.2 (s); 167.9 (s); 178.4 (s); MS *m/z* 465 (M+1, 4); 464 (M^+, 12); 434 (2); 378 (44); 347 (65); 214 (100); anal $C_{26}H_{28}N_2O_6 \cdot H_2O$ (C, H, N).

7-Cyclopentyloxycarbonylamino-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***11f***. Yield 56%; mp = 236–238 °C (from dichloromethane); IR (KBr): 1719, 1710, 1635 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.42–2.00 (m, 8H); 3.90 (s, 3H); 3.97 (s, 3H); 5.15–5.25 (brs, 1H); 5.30 (s, 2H); 6.33 (d, *J* = 7.6 Hz, 1H); 6.90 (brs, 1H); 6.99–7.06 (m, 2H); 7.53–7.65 (m, 3H); 7.90 (s, 1H); 8.35 (d, *J* = 8.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 23.0 (2t); 32.5 (2t); 51.8 (t); 52.2 (q); 55.5 (q); 78.1 (d); 103.0 (d); 109.2 (d); 111.1 (d); 115.5 (d); 121.8 (s); 122.0 (d); 127.3 (d); 127.8 (s); 128.1 (s); 131.2 (d); 141.2 (s); 142.8 (s); 144.4 (d); 153.4 (s); 156.9 (s); 166.6 (s); 178.1 (s); MS *m/z* 451 (M+1, 1); 450 (M^+, 3); 364 (22); 179 (100); anal $C_{25}H_{26}N_2O_6$ (C, H, N).

7-Cyclopentyloxycarbonylamino-1-(2-methoxy-4-methoxycarbonylbenzyl)-2-methyl-4-oxo-1,4-dihydroquinoline ***11g***. Yield 56%; mp = 176–178 °C (from dichloromethane); IR (KBr): 2958, 1721, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.50–1.95 (m, 8H); 2.63 (s, 3H); 3.85 (s, 6H); 5.15–5.20 (brs, 1H); 5.25 (s, 2H); 5.43–5.47 (brs, 1H); 6.55 (s, 1H); 7.45–7.49 (m, 2H); 7.60 (dd, *J* = 7.6 and 1.2 Hz, 1H); 7.88–8.07 (m, 3H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 22.4 (q); 23.5 (2t); 32.5 (2t); 52.2 (q); 55.6 (q); 66.2 (t); 78.4 (d); 100.9 (d); 109.0 (d); 110.9 (d); 114.7 (s); 119.2 (d); 122.0 (d); 123.0 (d); 127.8 (s); 128.0 (d); 131.4 (s); 143.0 (s); 143.4 (s); 153.3 (s); 156.4 (s); 156.7 (s); 164.2 (s); 166.3 (s); MS *m/z* 465 (M+1, 2); 464 (M^+, 7); 179 (100); anal $C_{26}H_{28}N_2O_6$ (C, H, N).

7-Cyclopentyloxycarbonylamino-1-(2-methoxy-4-methoxycarbonylbenzyl)-3-methyl-4-oxo-1,4-dihydroquinoline ***11h***. Elution with dichloromethane/methanol (98:2) gave **11h** (61%); mp = 159–161 °C (from ether/acetone); IR (KBr): 1723, 1628, 1575 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.50–1.95 (m, 8H); 2.13 (s, 3H); 3.90 (s, 3H); 3.97 (s, 3H); 5.05–5.10 (brs, 1H); 5.28 (s, 2H); 6.90 (d, *J* = 8.0 Hz, 1H); 7.05 (dd, *J* = 8.7 and 1.8 Hz, 1H); 7.13 (d, *J* = 1.8 Hz, 1H); 7.48–7.60 (m, 3H); 7.80 (d, *J* = 1.4 Hz, 1H); 8.37 (d, *J* = 8.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 13.8 (q); 23.5 (2t); 32.6 (2t); 50.9 (t); 52.2 (q); 55.6 (q); 76.3 (t); 103.3 (d); 111.0 (d); 114.6 (d); 108.2 (s); 121.6 (s); 122.0 (d); 126.8 (d); 128.0 (d); 128.6 (s); 131.5 (s); 140.6 (d); 142.0 (s); 143.1 (s); 152.6 (s); 156.3 (s); 166.2 (s); 177.8 (s); MS *m/z* 465 (M+1, 8); 464 (M^+, 24); 378 (23); 179 (100); anal $C_{26}H_{28}N_2O_6 \cdot H_2O$ (C, H, N).

7-Cyclopentyloxycarbonylamino-1-(4-methoxycarbonylbenzyl)-2-methyl-4-oxo-1,4-dihydroquinoline ***11i***. Elution with dichloromethane/methanol (98:2) gave **11i** (55%); mp = 190–192 °C (from dichloromethane); IR (KBr): 2956, 1723, 1604 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.50–1.90 (m, 8H); 2.97 (s, 3H); 3.95 (s, 3H); 5.20 (brs, 1H); 5.64 (s, 2H); 7.01 (s, 1H); 7.62 (d, *J* = 7.9 Hz, 2H); 8.00 (d, *J* = 7.6 Hz, 1H); 8.09 (d, *J* = 7.9 Hz, 2H); 8.22 (d, *J* = 7.6 Hz, 1H); 8.43 (s, 1H); 9.9 (brs, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 22.6 (2t); 31.7 (2t); 51.3 (q); 69.6 (t); 77.7 (d); 100.0 (d); 108.8 (d); 114.1 (s); 118.1 (d); 122.2 (d); 126.2 (2d); 129.2 (2d); 138.5 (s); 141.7 (s); 143.3 (s); 152.2 (s); 158.1 (s); 162.9 (s); 165.2 (s); MS *m/z* 435 (M+1, 3); 434 (M^+, 3); 322 (24); 149 (100); anal $C_{25}H_{26}N_2O_4 \cdot CH_2Cl_2$ (C, H, N).

7-Cyclopentyloxycarbonylamino-1-(4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***11j***. Elution with dichloromethane/methanol (98:2) gave **11j** (44%); mp = 187–189 °C (from dichloromethane); IR (KBr): 2960, 1723, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.40–1.88 (m, 8H); 3.88 (s, 3H); 5.10 (brs, 1H); 5.31 (s, 2H); 6.24 (d, *J* = 7.6 Hz, 1H); 7.22 (d, *J* = 7.8 Hz, 2H); 7.62 (d, *J* = 7.6 Hz, 1H); 7.94–7.96 (m, 3H); 8.29 (d, *J* = 8.8 Hz, 2H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 23.4 (2t); 32.6 (2t); 52.1 (q); 56.1 (t); 76.4 (d); 103.1 (d); 110.2 (d); 115.4 (d); 122.3 (s); 126.5 (2d); 127.7 (d); 129.9 (s); 130.2 (2d); 140.9 (s); 141.0 (s); 143.4 (d); 153.4 (s); 166.4 (s); 177.7 (s); MS *m/z* 421 (M+1, 4); 420 (M^+, 2); 334 (22); 308 (13); 149 (100); anal $C_{24}H_{24}N_2O_5 \cdot 1.5\ H_2O$ (C, H, N).

General procedure for preparation of compounds ***11c–e***

A mixture of the corresponding amine **10c–e** (1 mmol), cyclopentylacetic acid (1.05 mmol), 4-dimethylaminopyridine (1.05 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (1.05 mmol) was dissolved in dichloromethane (10 mL) under nitrogen. The mixture was stirred at room temperature for 24 h, poured into 1 N hydrochloric acid (10 mL) and extracted with dichloromethane (3 x 10 mL). The organic layer was washed with water and brine, then dried over Na_2SO_4, and evaporated. The product was purified by column chromatography using as eluent ether/acetone/diethylamine (70:30:5).

6-Cyclopentylacetamido-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***11c***. Yield 75%; mp = 231–234 °C (from dichloromethane); IR (KBr): 3286, 1725, 1681, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.20–2.00 (m, 8H); 2.30–2.50 (m, 1H); 2.52 (d, *J* = 7.3 Hz, 2H); 3.90 (s, 3H); 3.99 (s, 3H); 5.35 (s, 2H); 6.29 (d, *J* = 7.6 Hz, 1H); 6.80 (d, *J* = 7.8 Hz, 1H); 7.28 (d, *J* = 9.3 Hz, 1H); 7.51 (dd, *J* = 7.8 and 1.5 Hz, 1H); 7.61 (d, *J* = 1.5 Hz, 1H); 7.65 (d, *J* = 7.6 Hz, 1H); 8.48 (d, *J* = 2.6 Hz, 1H); 8.63 (dd, *J* = 9.3 and 2.6 Hz, 1H); 9.43 (brs, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 24.7 (2t); 32.2 (2t); 37.0 (d); 43.1 (t); 51.8 (t); 52.1 (q); 55.5 (q); 108.7 (d); 111.0 (d); 114.6 (d); 116.9 (d); 122.0 (d); 125.6 (d); 126.8 (d); 127.8 (s); 131.2 (s); 135.9 (s); 136.0 (s); 144.0 (d); 156.2 (s); 166.4 (s); 172.5 (s); 178.3 (s); MS *m/z* 449 (M+1, 9); 448 (M^+, 26); 179 (100); 151 (18); 149 (19); anal $C_{26}H_{28}N_2O_5$ (C, H, N).

5-Cyclopentylacetamido-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***11d***. Yield 71%; mp = 188–191 °C (from dichloromethane/methanol); IR (KBr): 3500, 1721, 1636, 1605 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.20–1.95 (m, 8H); 2.38–2.48 (m, 1H); 2.48 (d, *J* = 7.0 Hz, 2H); 3.91 (s, 3H); 3.99 (s, 3H); 5.31 (s, 2H); 6.31 (d, *J* = 7.6 Hz, 1H); 6.79 (d, *J* = 7.9 Hz, 1H); 6.87 (dd, *J* = 8.6 and 0.9 Hz, 1H);

7.47 (dd, J = 8.6 and 8.3 Hz, 1H); 7.53 (dd, J = 7.9 and 1.4 Hz, 1H); 7.60 (d, J = 7.6 Hz, 1H); 7.61 (d, J = 1.4 Hz, 1H); 8.67 (dd, J = 8.3 and 0.9 Hz, 1H); 13.88 (s, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 25.0 (2t); 32.6 (2t); 37.2 (d); 45.3 (t); 52.4 (q); 52.8 (t); 55.8 (q); 109.2 (d); 111.1 (d); 111.3 (d); 113.6 (d); 122.3 (d); 122.5 (s); 126.8 (d); 127.8 (s); 131.5 (s); 133.5 (d); 141.2 (s); 142.3 (s); 143.1 (d); 156.4 (s); 156.6 (s); 172.8 (s); 181.8 (s); MS *m/z* 449 (M+1, 9); 448 (M^+, 1); 368 (100); 179 (42).

7-Cyclopentylacetamido-1-(2-methoxy-4-methoxycarbonylbenzyl)-4-oxo-1,4-dihydroquinoline ***11e***. Yield 64%; mp = 216–218 °C (from dichloromethane/methanol); IR (KBr): 1719, 1612, 1561 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.20–2.00 (m, 8H); 2.20–2.40 (m, 3H); 3.90 (s, 3H); 3.96 (s, 3H); 5.31 (s, 2H); 6.28 (d, J = 7.8 Hz, 1H); 7.02 (dd, J = 9.5 and 1.1 Hz, 1H); 7.09 (d, J = 8.2 Hz, 1H); 7.50–7.60 (m, 2H); 7.64 (d, J = 7.8 Hz, 1H); 7.70 (brs, 1H); 8.33 (d, J = 8.7 Hz, 1H); 8.36 (brs, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 24.6 (2t); 32.1 (2t); 36.8 (d); 43.2 (t); 51.9 (t); 52.1 (q); 55.4 (q); 104.8 (d); 109.0 (d); 111.0 (d); 116.2 (d); 121.9 (d); 122.2 (s); 126.9 (d); 127.7 (s); 128.3 (d); 131.1 (s); 141.0 (s); 142.6 (s); 144.5 (d); 156.9 (s); 166.6 (s); 172.8 (s); 178.0 (s); MS *m/z* 448 (M^+, 1); 179 (10); 111 (10); 97 (22); 57 (100); anal $C_{26}H_{28}N_2O_5 \cdot H_2O$ (C, H, N).

General procedure for preparation of carboxylic acids ***12a–j***
A solution of lithium hydroxide monohydrate (5 mmol) in water (3.5 mL) was added to a stirred solution of the proper ester **11a–j** (1 mmol) in a mixture of methanol (10 mL) and tetrahydrofuran (8 mL). The mixture was stirred for 24 h at room temperature, concentrated under reduced pressure and the residue acidified with 1 N hydrochloric acid. The precipitate was isolated by filtration, washed with water and dried in vacuo. The obtained acid was used without further purification in the following step.

4-(6-Cyclopentyloxycarbonylamino-1-methyl-4-oxo-1,4-dihydro-2-quinolylmethyl)-3-methoxybenzoic acid ***12a***. Yield 37%; IR (KBr): 3480, 1703, 1641, 1573 cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.64–2.05 (m, 8H); 3.97 (s, 3H); 4.04 (s, 3H); 4.22 (s, 2H); 5.28 (m, 1H); 6.36 (s, 1H); 6.63 (brs, 1H); 7.34 (d, J = 7.4 Hz, 1H); 7.43 (d, J = 7.7 Hz, 1H); 8.00–8.21 (m, 3H); 8.57 (s, 1H).

4-(7-Cyclopentyloxycarbonylamino-1-methyl-4-oxo-1,4-dihydro-2-quinolylmethyl)-3-methoxybenzoic acid ***12b***. Yield 85%; IR (KBr): 1634, 1609, 1488, 1337, 1291 cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.80–2.10 (m, 8H); 3.99 (s, 3H); 4.30 (s, 3H); 4.67 (s, 2H); 5.30 (m, 1H); 6.73 (s, 1H); 7.41 (d, J = 8.0 Hz, 1H); 7.75–7.81 (m, 3H); 8.42 (d, J = 9.1 Hz, 1H); 8.70 (d, J = 1.4 Hz, 1H); 10.32 (s, 1H).

4-(6-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12c***. Yield 85%; mp = 264–266 °C (from methanol); IR (KBr): 3446, 1698, 1649, 1561 cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.30–1.41 (m, 2H); 1.62–1.82 (m, 4H); 1.90–2.10 (m, 2H); 2.35–2.80 (m, 1H); 2.50 (d, J = 7.3 Hz, 2H); 4.06 (s, 3H); 5.84 (s, 2H); 6.80 (d, J = 7.3 Hz, 1H); 7.14 (d, J = 7.9 Hz, 1H); 7.67 (dd, J = 7.9 and 1.4 Hz, 1H); 7.77 (d, J = 1.4 Hz, 1H); 7.91 (d, J = 9.4 Hz, 1H); 8.15 (dd, J = 9.4 and 2.5 Hz, 1H); 8.57 (d, J = 7.3 Hz, 1H); 8.72 (d, J = 2.5 Hz, 1H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 28.3 (2t); 35.8 (2t); 41.0 (d); 46.5 (t); 56.6 (t); 58.7 (q); 110.4 (d); 115.6 (d); 117.7 (d); 121.9 (d); 125.9 (d); 128.7 (s); 130.5 (d); 131.4 (s); 131.6 (d); 136.3 (s); 140.3 (s); 140.6 (s); 150.6 (d); 160.9 (s); 171.4 (s); 177.1 (s); 178.5 (s); MS *m/z* 435 (M+1, 4); 434 (M^+, 14); 165 (98); 160 (42); 137 (26); 135 (30); anal $C_{25}H_{26}N_2O_5 \cdot H_2O$ (C, H, N).

4-(5-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12d***. Yield 70%; mp = 129–134 °C (from methanol); IR (KBr): 3450, 2949, 1780, 1630, 1522 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.40–2.10 (m, 8H); 2.10–2.51 (m, 3H); 4.00 (s, 3H); 5.35 (s, 2H); 6.40 (d, J = 7.6 Hz, 1H); 6.80 (d, J = 8.0 Hz, 1H); 6.88 (d, J = 8.5 Hz, 1H); 7.49 (dd, J = 8.5 and 8.1 Hz, 1H); 7.58 (d, J = 1.4 Hz, 1H); 7.60–7.70 (m, 2H); 8.68 (d, J = 8.1 Hz, 1H); 13.90 (brs, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 24.6 (2t); 32.2 (2t); 36.9 (d); 44.9 (t); 52.6 (t); 55.4 (q); 109.9 (d); 110.3 (d); 111.2 (d); 113.4 (d); 114.5 (s); 122.2 (d); 126.5 (d); 127.1 (s); 132.1 (s); 133.3 (d); 141.0 (s); 141.2 (s); 143.8 (d); 156.1 (s); 168.1 (s); 173.0 (s); 181.5 (s); MS *m/z* 435 (M+1, 10); 434 (M^+, 36); 325 (24); 161 (100); anal $C_{25}H_{26}N_2O_5 \cdot MeOH$ (C, H, N).

4-(7-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12e***. Yield 85%; mp = 235–240 °C (from dichloromethane/methanol); IR (KBr): 3400, 3100, 1700, 1662, 1625, 1613 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.52–1.88 (m, 8H); 2.05–2.20 (m, 1H); 2.28 (d, J = 7.0 Hz, 2H); 3.95 (s, 3H); 5.36 (s, 2H); 6.05 (d, J = 7.8 Hz, 1H); 6.82 (d, J = 7.8 Hz, 1H); 7.43 (d, J = 8.2 Hz, 2H); 7.54 (s, 1H); 7.89 (s, 1H); 8.07 (d, J = 8.2 Hz, 2H); 10.20 (s, 1H); 12.50 (brs, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 24.7 (2t); 32.1 (2t); 36.7 (d); 42.8(t); 50.9 (t); 55.9 (q); 104.7 (d); 109.2 (d); 111.3 (d); 115.5 (d); 122.0 (d); 122.5 (s); 126.8 (d); 126.9 (d); 129.1 (s); 131.7 (s); 141.0 (s); 142.9 (s); 145.4 (d); 156.6 (s); 167.1 (s); 171.8 (s); 176.1 (s); MS *m/z* 435 (M+1, 37); 434 (M^+, 2); 299 (27); 271 (100); anal $C_{25}H_{26}N_2O_5 \cdot MeOH$ (C, H, N).

4-(7-Cyclopentyloxycarbonylamino-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12f***. Yield 97%; mp (dec) = 250 °C (from methanol); IR (KBr): 3530, 1702, 1628, 1614 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 1.55–2.00 (m, 8H); 3.92 (s, 3H); 5.13 (brs, 1H); 5.62 (s, 2H); 6.89 (d, J = 7.3 Hz, 1H); 7.24 (d, J = 7.7 Hz, 1H); 7.48 (d, J = 9.1 Hz, 1H); 7.57–7.60 (m, 2H); 8.26 (d, J = 9.1 Hz, 1H); 8.34 (s, 1H); 8.41 (d, J = 7.3 Hz, 1H); 9.75 (brs, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 23.1 (2t); 32.2 (2t); 53.3 (t); 55.2 (q); 78.1 (d); 102.6 (d); 105.9 (d); 111.3 (d); 118.0 (d); 118.1 (s); 122.0 (d); 125.8 (s); 126.1 (d); 128.8 (d); 132.3 (s); 140.9 (s); 144.8 (s); 147.0 (d); 153.4 (s); 156.9 (s); 167.5 (s); 172.7 (s); anal $C_{24}H_{24}N_2O_6 \cdot CH_2Cl_2$ (C, H, N).

4-(7-Cyclopentyloxycarbonylamino-2-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12g***. Yield 90%; mp = 188–190 °C (from methanol); IR (KBr): 3542, 1691, 1605 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 1.50–1.95 (m, 8H); 2.71 (s, 3H); 3.81 (s, 3H); 5.10 (brs, 1H); 5.47 (s, 2H); 7.21 (s, 1H); 7.40 (dd, J = 9.2 and 2.2 Hz, 1H); 7.49–7.60 (m, 3H); 8.07 (d, J = 9.2 Hz, 1H); 8.35 (d, J = 1.8 Hz, 1H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 20.9 (q); 24.6 (2t); 30.7 (2t); 56.3 (q); 69.0 (t); 70.8 (d); 103.4 (d); 105.4 (d); 112.5 (d); 115.8 (s); 121.4 (2d); 123.3 (d); 125.6 (d); 128.7 (s); 130.2 (d); 134.9 (s); 142.0 (s); 146.8 (s); 158.7 (s); 159.9 (s); 168.8 (s).

4-(7-Cyclopentyloxycarbonylamino-3-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoic acid ***12h***. Yield 97%; mp = 207–209 °C (from dichloromethane/methanol); IR (KBr): 3420, 1721, 1685, 1631 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 1.60–2.05 (m, 8H); 2.53 (s, 3H); 4.06 (s, 3H); 5.25 (brs, 1H); 5.89 (s, 2H); 7.24 (d, J = 8.0 Hz, 1H);

7.55–7.66 (m, 2H); 7.71 (d, J = 1.0 Hz, 1H); 8.39 (s, 1H); 8.48 (d, J = 9.2, 1H); 8.48 (d, J = 1.6 Hz, 1H); 8.98 (s, 1H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 13.8 (q); 24.6 (2t); 33.7 (2t); 55.4 (t); 56.4 (q); 79.8 (d); 104.1 (d); 112.7 (d); 118.0 (s); 120.5 (d); 123.2 (d); 126.8 (d); 128.0 (s); 129.7 (d); 133.8 (s); 141.8 (s); 146.4 (s); 150.8 (d); 155.0 (s); 158.6 (s); 168.9 (s); 169.9 (s).

4-(7-Cyclopentyloxycarbonylamino-2-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoic acid ***12i***. Yield 80 %; mp = 198–200 °C (from dichloromethane/methanol); IR (KBr): 3450, 2925, 1740, 1694, 1604 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 200 MHz) δ: 1.50–1.95 (m, 8H); 2.84 (s, 3H); 5.20 (brs, 1H); 5.68 (s, 2H); 7.52 (s, 1H); 7.71 (d, J = 8.4 Hz, 2H); 8.02 (d, J = 8.4 Hz, 2H); 8.11 (dd, J = 9.6 and 1.8 Hz, 1H); 8.28 (d, J = 9.6 Hz, 1H); 8.33 (d, J = 1.8 Hz, 1H); 11.00 (s, 1H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 21.2 (2t); 33.7 (2t); 73.2 (t); 81.7 (d); 104.0 (d); 106.0 (d); 116.0 (s); 120.7 (d); 124.1 (d); 128.7 (2d); 131.2 (2d); 132.2 (s); 140.7 (s); 141.0 (s); 148.7 (s); 155.2 (s); 160.4 (s); MS *m/z* 421 (M+1, 1); 420 (M$^+$, 2); 286 (60); 218 (95); 135 (100).

4-(7-Cyclopentyloxycarbonylamino-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoic acid ***12j***. Yield 83%; mp = 190–192 °C (from dichloromethane/methanol); IR (KBr): 3245, 1726, 1615 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 1.60–2.00 (m, 8H); 5.12 (brs, 1H); 5.78 (s, 2H); 6.76 (d, J = 7.2 Hz, 1H); 7.42–7.49 (m, 3H); 8.06 (d, J = 8.2 Hz, 1H); 8.30–8.35 (m, 2H); 8.61 (d, J = 7.2 Hz, 1H); 9.98 (s, 1H); ^{13}C-NMR (CD_3OD, 50 MHz) δ: 23.5 (2t); 32.5 (2t); 56.0 (t); 77.7 (d); 103.6 (d); 107.8 (d); 116.5 (d); 120.1 (d); 126.8 (d); 127.0 (2d); 130.1 (2d); 130.6 (s); 140.8 (s); 141.0 (s); 144.1 (s); 147.1 (d); 153.4 (s); 167.2 (s); 173.9 (s); MS *m/z* 406 (M$^+$, 2); 135 (50); 57 (100).

3-Methoxy-4-(7-nitro-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoic acid ***12k***. A solution of lithium hydroxide monohydrate (263 mg, 6.25 mmol) in water (3.5 mL) was added to a stirred solution of **8g** (460 mg, 1.25 mmol) in a mixture of methanol (10 mL) and tetrahydrofuran (8 mL). The mixture was refluxed for 30 min, concentrated under reduced pressure, and the residue was acidified with 1 N hydrochloric acid. The precipitate was isolated by filtration, washed with water, and dried in vacuo to afford **12k** (96%); mp (dec) = 274–276 °C (from methanol); IR (KBr): 3400, 1685, 1637, 1521, 1346 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 200 MHz) δ: 4.05 (s, 3H); 5.46 (s, 2H); 6.47 (d, J = 7.8 Hz, 1H); 7.10 (d, J = 7.8 Hz, 1H); 7.63 (dd, J = 7.8 and 1.4 Hz, 1H); 7.68 (d, J = 1.4 Hz, 1H); 7.96 (d, J = 7.8 Hz, 1H); 8.16 (dd, J = 8.9 and 2.0 Hz, 1H); 8.50 (d, J = 2.0 Hz, 1H); 8.59 (d, J = 8.9 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 51.8 (t); 55.7 (q); 111.3 (d); 111.8 (d); 112.6 (d); 117.6 (d); 122.5 (d); 126.6 (s); 127.8 (d); 128.9 (d); 130.0 (s); 132.6 (s); 139.7 (s); 145.9 (d); 156.5 (s); 167.8 (s); 177.5 (s); MS *m/z* 355 (M+1, 6); 354 (M$^+$, 6); 165 (100); 137 (18); 135 (23); anal $C_{18}H_{14}N_2O_6 \cdot H_2O$ (C, H, N).

General procedure for preparation of compounds ***13a–k***

A mixture of the corresponding carboxylic acid **12a–k** (1 mmol), 2-toluenesulfonamide (1.05 mmol), 4-dimethylaminopyridine (1.05 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (1.05 mmol) was dissolved in dry dichloromethane (15 mL) under nitrogen. The mixture was stirred for 24 h, poured into 1 N hydrochloric acid (15 mL) and extracted with dichloromethane (3 x 10 mL). The extracts were washed with water and brine, dried over Na_2SO_4 and evaporated. The residue was purified by chromatography.

N-[4-(6-Cyclopentyloxycarbonylamino-1-methyl-4-oxo-1,4-dihydro-2-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13a***. Yield 14%; mp = 238–240 °C (from ether/acetone); IR (KBr): 1720, 1604, 1434 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 1.59–1.89 (m, 8H); 2.72 (s, 3H); 3.61 (s, 3H); 3.83 (s, 3H); 4.01 (s, 2H); 5.18 (m, 1H); 6.09 (brs, 1H); 6.89 (d, J = 7.0 Hz, 1H); 7.16–7.29 (m, 2H); 7.39–7.50 (m, 4H); 8.10 (s, 1H); 8.27–8.31 (m, 2H); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ: 20.4 (q); 23.6 (2t); 32.7 (2t); 34.4 (t); 34.7 (q); 55.8 (q); 78.3 (d); 110.8 (d); 111.6 (d); 114.3 (d); 116.6 (d); 120.8 (d); 124.2 (d); 126.1 (d); 126.7 (s); 128.1 (s); 128.8 (s); 129.6 (s); 131.3 (d); 132.3 (d); 133.5 (s); 135.1 (d); 137.3 (s); 137.9 (s); 152.3 (s); 153.7 (s); 156.6 (s); 165.3 (s); 176.9 (s); 177.5 (s); anal $C_{32}H_{33}N_3O_7S \cdot 2.5\ H_2O$ (C, H, N).

N-[4-(7-Cyclopentyloxycarbonylamino-1-methyl-4-oxo-1,4-dihydro-2-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13b***. Yield 60%; mp = 138–140 °C (from ether/acetone); IR (KBr): 1700, 1627, 1603, 1459, 1453 cm^{-1}; ^{1}H-NMR (CD_3OD, 300 MHz) δ: 1.70–2.05 (m, 8H); 2.78 (s, 3H); 3.97 (s, 3H); 4.24 (s, 3H); 4.63 (s, 2H); 5.35 (brs, 1H); 6.67 (s, 1H); 7.40 (d, J = 7.7 Hz, 1H); 7.48 (d, J = 7.8 Hz, 1H); 7.53 (d, J = 7.7 Hz, 1H); 7.59–7.66 (m, 3H); 7.74 (dd, J = 9.1 and 1.7 Hz, 1H); 8.25 (dd, J = 7.9 and 1.2 Hz, 1H); 8.40 (d, J = 9.1 Hz, 1H); 8.66 (d, J = 1.7 Hz, 1H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 20.3 (q); 24.6 (2t); 30.8 (2t); 33.7 (t); 36.3 (q); 56.4 (q); 80.0 (d); 104.6 (d); 107.0 (d); 111.6 (d); 116.9 (s); 120.3 (d); 122.1 (d); 126.8 (d); 127.2 (d); 130.1 (s); 132.1 (d); 132.3 (d); 133.5 (d); 134.5 (s); 134.9 (d); 138.8 (s); 138.9 (s); 144.7 (s); 147.6 (s); 155.2 (s); 158.9 (s); 161.5 (s); 166.8 (s); 169.8 (s); anal $C_{32}H_{33}N_3O_7S$ (C, H, N).

N-[4-(6-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13c***. Yield 40%; mp = 261–263 °C (from dichloromethane/methanol); IR (KBr): 3300, 1612, 1592, 1538 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.20–2.00 (m, 8H); 2.20–2.50 (m, 3H); 2.69 (s, 3H); 3.89 (s, 3H); 5.36 (s, 2H); 6.36 (d, J = 7.4 Hz, 1H); 6.71 (d, J = 7.7 Hz, 1H); 7.26–7.56 (m, 6H); 7.76 (d, J = 7.4 Hz, 1H); 7.92 (d, J = 2.4 Hz, 1H); 8.16 (d, J = 7.7 Hz, 1H); 8.46 (dd, J = 9.3 and 2.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 19.7 (q); 24.6 (2t); 32.1 (2t); 37.0 (d); 43.0 (t); 51.8 (t); 55.4 (q); 108.5 (d); 110.5 (d); 114.7 (d); 116.9 (d); 120.6 (d); 125.7 (2d); 126.7 (2d); 132.0 (d); 132.9 (d); 135.6 (s); 136.1 (s); 137.2 (s); 144.3 (d); 156.3 (s); 172.8 (s); 178.4 (s); anal $C_{32}H_{33}N_3O_6S \cdot CH_2Cl_2$ (C, H, N).

N-[4-(5-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13d***. Yield 60%; mp = 268–270 °C (from dichloromethane/methanol); IR (KBr): 3400, 1700, 1625, 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 200 MHz) δ: 1.20–2.00 (m, 8H); 2.13–2.45 (m, 3H); 2.69 (s, 3H); 3.92 (s, 3H); 5.29 (s, 2H); 6.28 (d, J = 7.5 Hz, 1H); 6.62 (d, J = 8.0 Hz, 1H); 6.78 (d, J = 8.7 Hz, 1H); 7.25–7.50 (m, 6H); 7.60 (d, J = 7.5 Hz, 1H); 8.26 (d, J = 8.0 Hz, 1H); 8.60 (d, J = 8.0 Hz, 1H); 13.74 (s, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 19.8 (q); 24.7 (2t); 32.3 (2t); 37.0 (d); 45.0 (t); 52.5 (t); 55.6 (q); 109.7 (d); 110.4 (d); 110.5 (d); 113.5 (d); 114.6 (s); 120.3 (d); 126.0 (d); 126.6 (d); 127.8 (s); 130.8 (d); 132.2 (d); 133.4 (d); 133.5 (d); 137.0 (s); 137.3 (s); 140.9 (s); 141.4 (s); 143.7 (d); 156.5 (s); 165.3 (s); 173.0 (s); 181.6 (s); anal $C_{32}H_{33}N_3O_5S \cdot 3\ H_2O$ (C, H, N).

N-[4-(7-Cyclopentylacetamido-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13e***. Yield 32%; mp = 258–260 °C (from dichloromethane/methanol);

IR (KBr): 3400, 1614, 1563, 1519 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.12–1.95 (m, 8H); 2.20–2.50 (m, 3H); 2.70 (s, 3H); 3.92 (s, 3H); 5.35 (s, 2H); 6.34 (d, *J* = 7.7 Hz, 1H); 7.07–7.52 (m, 8H); 7.82 (d, *J* = 7.7 Hz, 1H); 8.21 (brs, 1H); 8.26 (d, *J* = 8.8 Hz, 1H); 8.39 (d, *J* = 1.7 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 19.9 (q); 24.7 (2t); 32.3 (2t); 37.1 (d); 43.5 (t); 52.3 (t); 55.5 (q); 105.3 (d); 109.2 (d); 110.4 (d); 116.4 (d); 120.3 (d); 122.5 (s); 126.0 (d); 127.1 (s); 127.7 (s); 128.1 (d); 128.4 (d); 130.9 (d); 132.2 (d); 133.4 (d); 133.5 (s); 137.3 (s); 137.4 (s); 141.0 (s); 142.3 (s); 144.9 (d); 157.1 (s); 165.9 (s); 174.1 (s); 178.1 (s); anal $C_{32}H_{33}N_3O_6S \cdot 3\ H_2O$ (C, H, N, S).

N-[4-(7-Cyclopentyloxycarbonylamino-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13f***. Yield 25%; mp = 206–208 °C (from dichloromethane/methanol); IR (KBr): 1748, 1690, 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 1.60–2.00 (m, 8H); 2.67 (s, 3H); 3.89 (s, 3H); 5.20 (brs, 1H); 5.68 (s, 2H); 7.14 (d, *J* = 7.2 Hz, 1H); 7.28–7.53 (m, 7H); 8.21 (d, *J* = 7.9 Hz, 1H); 8.26 (d, *J* = 9.0 Hz, 1H), 8.39 (s, 1H); 8.62 (d, *J* = 7.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 19.7 (q); 23.4 (2t); 32.5 (2t); 53.7 (t); 55.6 (q); 78.5 (d); 102.7 (d); 105.3 (d); 110.6 (d); 117.4 (s); 118.9 (d); 120.3 (d); 126.0 (d); 126.2 (d); 129.6 (d); 131.0 (d); 132.2 (d); 133.6 (d); 133.7 (s); 136.8 (s); 137.4 (s); 141.1 (s); 145.4 (s); 148.1 (d); 153.5 (s); 157.5 (s); 165.1 (s); 171.1 (s); anal $C_{31}H_{31}N_3O_7S \cdot CH_2Cl_2$ (C, H, N).

N-[4-(7-Cyclopentyloxycarbonylamino-2-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13g***. Yield 30%; mp = 220–222 °C (from dichloromethane/methanol); IR (KBr): 1737, 1696, 1648 cm^{-1}; ^{1}H-NMR (CD_3OD, 200 MHz) δ: 1.60–2.00 (m, 8H); 2.78 (s, 3H); 2.93 (s, 3H); 4.03 (s, 3H); 5.30 (brs, 1H); 5.72 (s, 2H); 7.44 (d, 1H); 7.47–7.78 (m, 7H); 8.26 (dd, *J* = 8.0 and 1.6 Hz, 1H); 8.31 (d, *J* = 9.2 Hz, 1H), 8.62 (d, *J* = 2.2 Hz, 1H); ^{13}C-NMR (CD_3OD, 75 MHz) δ: 20.3 (q); 20.8 (q); 24.6 (2t); 33.7 (2t); 56.5 (q), 68.8 (t); 79.9 (d); 103.4 (d); 105.5 (d), 111.4 (d); 115.8 (s); 121.5 (d); 121.7 (d); 125.3 (d); 127.2 (d); 129.1 (s); 130.5 (d); 130.5 (s); 132.2 (d); 133.5 (d); 134.8 (d); 134.9 (s); 139.0 (s); 142.0 (s); 146.7 (s); 155.1 (s); 158.9 (s); 160.0 (s); 168.7 (s); anal $C_{32}H_{33}N_3O_7S \cdot CH_2Cl_2$ (C, H, N, S).

N-[4-(7-Cyclopentyloxycarbonylamino-3-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)-3-methoxybenzoyl]-2-methylbenzenesulfonamide ***13h***. Yield 41%; mp = 218–220 °C (from dichloromethane); IR (KBr): 1700, 1629, 1573 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 1.50–1.95 (m, 8H); 2.13 (s, 3H); 2.65 (s, 3H); 3.92 (s, 3H); 5.13 (brs, 1H); 5.32 (s, 2H); 6.91 (d, *J* = 7.9 Hz, 1H); 7.03 (dd, *J* = 8.8 Hz and 1.5 Hz, 1H), 7.27–7.37 (m, 2H); 7.40 (d, *J* = 7.9 Hz, 1H); 7.43 (d, *J* = 1.5 Hz, 1H); 7.50 (dd, *J* = 7.50 Hz, 1H); 7.67 (s, 1H); 7.86 (br, 1H); 8.22 (d, *J* = 8.2 Hz, 1H); 8.26 (d, *J* = 8.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz) δ: 13.6 (q); 19.9 (q); 23.4 (2t); 32.6 (2t); 51.2 (t); 55.6 (q); 78.2 (d); 110.3 (d); 115.2 (d); 118.2 (s); 120.0 (d); 120.8 (s); 126.1 (d); 127.5 (2d); 128.6 (s); 131.3 (d); 132.2 (d); 132.7 (s); 133.6 (d); 136.9 (s); 137.4 (s); 141.0 (s); 142.1 (s); 142.2 (d); 153.8 (s); 157.2 (s); 165.1 (s); 177.9 (s); anal $C_{32}H_{33}N_3O_7S$ (C, H, N, S).

N-[4-(7-Cyclopentyloxycarbonylamino-2-methyl-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoyl]-2-methylbenzenesulfonamide ***13i***. Yield 79%; mp = 228–230 °C (dichloromethane); IR (KBr): 1750, 1665, 1604 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.50–2.00 (m, 8H), 2.61 (s, 3H); 2,81 (s, 3H); 5.15 (brs, 1H); 5.65 (s, 2H), 7.40 (d, *J* = 7.7 Hz, 1H); 7.45–7.47 (m, 2H); 7.58 (ddd. *J* = 7.5, 7.5 and 1.3 Hz, 1H); 7.67–7.74 (m, 3H); 7.96 (d, *J* = 8.3 Hz, 2H); 8.04 (dd, *J* = 7.7 and 1,4 Hz, 1H); 8.22 (d, *J* = 9.2 Hz, 1H); 8.46 (d, *J* = 1.4 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 19.8 (q); 20.7 (q); 23.5 (2t); 32.5 (2t); 71.3 (t); 78.0 (d); 102.9 (d); 104.8 (d); 114.1 (s); 120.4 (d); 124.1 (d); 126.5 (d); 128.0 (2d); 129.0 (2d); 129.9 (s); 130.7 (d); 131.8 (s); 132.6 (d); 133.8 (d); 137.1 (s); 137.7 (s); 140.2 (s); 140.4 (s); 144.8 (s); 153.4 (s); 158.9 (s); 165.2 (s); 166.2 (s); anal $C_{31}H_{31}N_3O_6S \cdot CH_2Cl_2$ (C, H, N, S).

N-[4-(7-Cyclopentyloxycarbonylamino-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoyl]-2-methylbenzenesulfonamide ***13j***. Yield 77%; mp = 211–213 °C (from dichloromethane/methanol); IR (KBr): 1722, 1700, 1613 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 1.56–1.82 (m, 8H); 2.56 (s, 3H); 2.10 (m, 1H); 5.76 (s, 2H); 7.17–7.19 (m, 2H); 7.28–7.31 (m, 4H); 7.39 (dd, *J* = 7.4 and 6.8 Hz, 1H); 7.62 (d, *J* = 9.1 Hz, 1H); 7.69 (d, *J* = 7.9 Hz, 2H); 8.09 (d, *J* = 7.5 Hz, 1H); 8.13–8.16 (m, 2H); 8.92 (brs, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 19.8 (q); 23.4 (2t); 32.5 (2t); 58.2 (t); 78.7 (d); 102.9 (d); 104.9 (d); 116.4 (s); 119.8 (d); 126.0 (d); 126.2 (d); 127.4 (2d); 128.9 (2d); 131.0 (d); 132.1 (s); 132.2 (d); 133.6 (d); 136.8 (s); 137.5 (s); 138.0 (s); 140.8 (s); 146.2 (s); 149.0 (d); 153.6 (s); 165.1 (s); 169.6 (s); anal $C_{30}H_{29}N_3O_6S \cdot CH_2Cl_2$ (C, H, N, S).

N-[3-Methoxy-4-(7-nitro-4-oxo-1,4-dihydro-1-quinolylmethyl)benzoyl]-2-methylbenzenesulfonamide ***13k***. Yield 37%; mp = 296–298 °C (from dichloromethane/methanol); IR (KBr): 3450, 1690, 1638, 1596, 1464 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 2.67 (s, 3H); 3.97 (s, 3H); 5.40 (s, 2H); 6.44 (d, *J* = 7.9 Hz, 1H); 7.04 (d, *J* = 7.8 Hz, 1H); 7.26–7.48 (m, 5H); 7.57 (s, 1H); 7.88 (d, *J* = 7.9 Hz, 1H); 8.12 (dd, *J* = 8.8 and 1.7 Hz, 1H); 8.41 (d, *J* = 1.7 Hz, 1H); 8.57 (dd, *J* = 8.8 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 20.3 (q); 50.8 (t); 55.7 (q); 110.6 (d); 110.8 (d); 113.4 (d); 117.3 (d); 121.1 (d); 125.0 (d); 127.5 (d); 128.2 (d); 128.9 (d); 130.0 (s); 130.2 (s); 130.4 (s); 131.2 (2d); 136.0 (s); 139.9 (s); 147.2 (d); 149.4 (s); 156.2 (s); 175.6 (s); anal $C_{25}H_{21}N_3O_7S$ (C, H, N).

*Ethyl 8-acetamido-4-oxo-4H-benzo*pyran-*2-carboxylate* ***15***. A solution of 3-acetamido-2-hydroxyacetophenone **14** [30] (3 g, 15.5 mmol) and diethyl oxalate (4.5 g, 31.1 mmol) in dry tetrahydrofuran (40 mL) was added slowly to a stirred solution of sodium ethoxide (4.2 g, 62.2 mmol) in anhydrous ethanol (25 mL) under nitrogen. The mixture was refluxed for 3 h, acidified with 0.1 N hydrochloric acid, and extracted with chloroform. The organic layer was dried over Na_2SO_4 and evaporated. The residue was dissolved in a mixture of tetrahydrofuran/ethanol (1:1) (100 mL); hydrochloric acid (1.25 mL) was added, and refluxed for 1.5 h under nitrogen. The precipitate was collected by filtration to give **15** (2.28 g, 56%); mp = 216–217 °C (from dichloromethane); IR (KBr): 3279, 1728, 1668, 1541 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 1.46 (t, *J* = 7.0 Hz, 3H); 2.33 (s, 3H); 4.48 (q, *J* = 7.0 Hz, 2H); 7.11 (s, 1H); 7.43 (dd, *J* = 8.0 and 8.2 Hz, 1H); 7.86 (dd, *J* = 8.0 and 1.4 Hz, 1H); 8.13 (brs, 1H); 8.74 (dd, *J* = 8.2 and 1.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 14.5 (q); 25.3 (q); 63.7 (t); 115.4 (d); 120.1 (d); 124.6 (s); 125.4 (d); 126.6 (d); 128.6 (s); 151.3 (s); 161.0 (s); 169.8 (s); 178.4 (s); MS *m/z* 276 (M+1, 2); 275 (M^+, 7); 233 (100); 205 (64); 135 (11); anal $C_{14}H_{13}NO_5 \cdot$ MeOH (C, H, N).

Methyl 8-amino-4-oxo-4H-benzopyran-2-carboxylate ***16***. Ethyl 8-acetamido-4-oxo-4*H*-benzopyran-2-carboxylate **15** (0.51 g, 1.8 mmol) was dissolved in MeOH/HCl (50 mL) and the solution refluxed for 22 h. The solvent was removed under reduced pressure and the product was purified by column chromato-

graphy. Elution with dichloromethane gave **16** (0.2 g, 90%), mp = 128–130 °C (from dichloromethane); IR (NaCl): 3300, 1742, 1657, 1630, 1584 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz) δ: 4.01 (s, 3H); 7.04 (dd, J = 7.8 and 1.6 Hz, 1H); 7.08 (s, 1H); 7.23 (dd, J = 7.9 and 7.8 Hz, 1H); 7.52 (dd, J = 7.9 and 1.6 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 54.0 (q); 114.7 (d); 115.1 (d); 119.4 (d); 125.3 (s); 126.5 (d); 136.5 (s); MS *m/z* 220 (M+1, 13); 219 (M^+, 100); 135 (27); 131 (14); anal $C_{11}H_9NO_4 \cdot 0.5\ H_2O$ (C, H, N).

1-Methyl-4-oxo-2-(3-phenylpropyl)-1,4-dihydroquinoline-6-carboxylic acid ***17***. A solution of lithium hydroxide monohydrate (550 mg, 13.1 mmol) in water (8 mL) was added to a stirred solution of **2o** (840 mg, 2.6 mmol) in a mixture of methanol (14 mL) and tetrahydrofuran (11 mL). The mixture was refluxed for 30 min, concentrated under reduced pressure, and the residue acidified with 1 N hydrochloric acid. The precipitate was isolated by filtration, washed with water, and dried in vacuo to afford **17** (90%) mp = 280–281 °C (from dichloromethane); IR (KBr): 3450, 1699, 1628, 1594 cm^{-1}; ^{1}H-NMR ($CDCl_3$ + CD_3OD, 300 MHz) δ: 2.03–2.10 (m, 2H); 2.79–2.83 (m, 4H); 3.75 (s, 3H); 6.33 (s, 1H); 7.22–7.35 (m, 5H); 7.69 (d, J = 9.2 Hz, 1H); 8.28 (dd, J = 9.2 and 2.1 Hz, 1H); 8.74 (d, J = 2.1 Hz, 1H); ^{13}C-NMR ($CDCl_3$ + CD_3OD, 75 MHz) δ: 29.8 (t); 33.7 (t); 34.4 (q); 34.8 (t); 111.2 (d); 116.3 (d); 124.9 (d); 126.1 (d); 128.1 (2d); 128.3 (d); 131.9 (d); 140.3 (s); 143.5 (s); 156.4 (s); 169.0 (s); 177.9 (s); MS *m/z* (322 (M+1, 1); 321 (M^+, 2); 217 (100); 188 (12); 144 (12); anal $C_{20}H_{19}NO_3 \cdot 0.5\ H_2O$ (C, H, N).

Methyl 8-[1-methyl-4-oxo-2-(3-phenylpropyl)-1,4-dihydro-6-quinolylcarboxamido]-4-oxo-4H-benzopyran-2-carboxylate ***18***. A mixture of **17** (493 mg, 1.5 mmol), **16** (321 mg, 1.6 mmol), 4-dimethylaminopyridine (189 mg, 1.5 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (298 mg, 1.6 mmol) in dichloromethane (25 mL), under nitrogen was stirred during 24 h. The reaction mixture was poured into 1 N hydrochloric acid (35 mL) and extracted with dichloromethane (3 x 10 mL). The organic extracts were washed with water and brine, then dried over Na_2SO_4 and evaporated. The product was purified by column chromatography. Elution with dichloromethane/methanol (99:1) gave **18** (171 mg, 22%); mp = 222–223 °C (from dichloromethane); IR (NaCl): 3580, 1738, 1676, 1653, 1637, 1531 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.94–2.03 (m, 2H); 2.62–2.81 (m, 4H); 3.67 (s, 3H); 4.18 (s, 3H); 6.33 (s, 1H); 7.20 (s, 1H); 7.24–7.34 (m, 5H); 7.50 (dd, J = 7.8 and 8.0 Hz, 1H); 7.67 (d, J = 9.2 Hz, 1H); 7.93 (dd, J = 8.0 and 1.4 Hz, 1H); 8.46 (dd, J = 8.8 and 2.6 Hz, 1H); 8.95 (dd, J = 8.0 and 1.4 Hz, 1H); 9.02 (d, J = 2.6 Hz, 1H); 9.15 (s, 1H); ^{13}C-NMR ($CDCl_3$, 50 MHz) δ: 29.7 (t), 33.7 (t); 34.2 (q) ; 35.0 (t); 54.1 (q); 111.8 (d); 114.7 (d); 116.5 (d); 119.7 (d); 124.0 (s); 124.1 (d); 125.0 (d); 125.6 (s); 125.9 (d); 126.3 (d); 128.0 (s); 128.0 (s); 128.3 (d); 128.5 (d); 131.9 (d); 140.4 (s); 144.0 (s); 151.1 (s); 155.1 (s); 160.6 (s); 163.3 (s); 177.0 (s); 177.6 (s); MS *m/z* 510 (M+1-Me, 1); 509 (M–15, 2); 379 (100); 294 (9); 234 (29); anal $C_{31}H_{26}N_2O_6 \cdot H_2O$ (C, H, N).

*8-[1-Methyl-4-oxo-2-(3-phenylpropyl)-1,4-dihydro-6-quinolylcarboxamido]-4-oxo-4H-benzo*pyran-*2-carboxylic acid* ***19***. A solution of lithium hydroxide monohydrate (11 mg, 0.3 mmol) in water (1 mL) was added to a stirred solution of **18** (137 mg, 0.3 mmol) in a mixture of methanol (10 mL) and tetrahydrofuran (10 mL). The mixture was stirred for 24 h at room temperature, concentrated under reduced pressure and the residue acidified with 1 N hydrochloric acid. The precipitate was isolated by filtration, washed with water, and dried in vacuo to afford **19** (74%); mp = 289–290 °C (from dichloromethane/methanol); IR (KBr): 3428, 1667, 1654, 1633, 1542 cm^{-1}; ^{1}H-NMR (DMSO-d_6, 300 MHz) δ: 1.94–2.07 (m, 2H), 2.71–2.75 (m, 2H); 2.81–2.86 (m, 2H); 3.79 (s, 3H); 6.15 (s, 1H); 6.67 (s, 1H); 7.21–7.32 (m, 5H); 7.48 (dd, J = 7.9 and 7.8 Hz, 1H); 7.87 (dd, J = 8.0 and 1.7 Hz, 1H); 7.94 (d, J = 9.3 Hz, 1H); 8.06 (dd, J = 7.7 and 1.7 Hz, 1H); 8.38 (dd, J = 9.0 and 1.7 Hz, 1H); 8.92 (d, J =1.9 Hz, 1H); 10.52 (s, 1H); ^{13}C-NMR (DMSO-d_6, 75 MHz) δ: 30.0 (t); 33.7 (t); 34.8 (t); 34.9 (q); 111.1 (d); 113.4 (d); 117.8 (d); 122.0 (d); 124.7 (s); 125.7 (d); 125.8 (d); 125.9 (d); 126.3 (d); 128.0 (s); 128.2 (s); 128.5 (d); 128.7 (d); 129.3 (s); 131.2 (d); 131.8 (s); 141.7 (s); 144.2 (s); 150.0 (s); 156.2 (s); 161.5 (s); 165.0 (s); 176.2 (s); 177.9 (s); MS *m/z* 446 (14); 335 (5); 231 (100); anal $C_{30}H_{24}N_2O_6 \cdot CH_2Cl_2$ (C, H, N).

Pharmacology

The activity was assessed in vitro on [^{3}H]LTD_4 binding using guinea pig lung membranes (K_i) and by measuring the inhibition of LTD_4-induced guinea pig ileum contractions.

Radioligand binding assay of [^{3}H]LTD_4

Membrane fractions containing the LTD_4 receptors were prepared with minor modifications following the method described by Mong et al [46]. Incubations were carried out in 10 mM PIPES buffer (pH 7.4) containing 10 mM $CaCl_2$, 10 mM $MgCl_2$, 2 mM cysteine and 2 mM glycine. In drug competition assays, incubation mixtures (0.31 mL) containing 0.5 nM [^{3}H]LTD_4, receptor protein (150 μg/mL) and competing agents (agonists, antagonists or vehicle) were incubated at 25 °C for 30 min with or without 1 μM LTD_4. Separation of receptor-bound from free [^{3}H]LTD_4 was carried out by dilution in ice-cold buffer (4 mL 10 mM Tris–HCl; pH 7.4/100 mM NaCl) and immediate filtration under vacuum. The radioactivity retained on rinsed filters was determined by a liquid scintillation counter. Specific binding was defined as the difference between total binding and binding in the presence of 1 μM LTD_4 (non-specific binding). Data from drug competition experiments were analyzed by a non-linear least-squares regression analysis and the binding constant (K_i) was calculated using the Cheng–Prusoff equation [47].

LTD_4-induced contraction on guinea pig ileum[1]

Segments of ileum at least 2–3 cm in length taken from male Dunkin–Hartley guinea pigs (300–350 g) were suspended under 0.5 *g* tension in 5-mL organ baths containing Tyrode solution at 37 °C aerated with 5% CO_2–95% O_2. The bath fluid also contained indomethacin (3.3 μM) and atropin (1 μM) to remove the influence of intrinsic cyclooxygenase products and the cholinergic responses. After a 45-min equilibration period, the tissues were challenged with 3 nM LTD_4. Following washout and reequilibration, the tissues were again exposed to LTD_4. After obtaining reproducible control responses to LTD_4, the test compound was added to the organ bath 2.5 min prior to being challenged with LTD_4. Several concentrations of the compound were tested and the IC_{50} value was calculated (molar concentration of antagonist that reduced maximal contraction by 50%).

[1]Modification of procedure described in ref [15] by Cabré et al (1995) *Proc 95 World Congr on Inflammation*, Brighton, UK

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References

1 Borgeat P, Samuelsson B (1979) *J Biol Chem* 254 (16), 7865–7869
2 Hammarstrom S, Murphy R, Samuelsson B, Clark DA, Mioskowski CCh, Corey EJ (1979) *Biochem Biophys Res Commun* 91, 1266–1272
3 Borgeat P, Samuelsson B (1979) *Proc Natl Acad Sci USA* 76 (5), 2148–2152
4 Borgeat P, Samuelsson B (1979) *J Biol Chem* 254, 2643–2646
5 Ar JP, Lee TH (1993) *Clin Sci* 84, 501–510
6 Hay DWP, Torphy TJ, Undem BJ (1995) *Trends Pharmacol Sci* 16, 304–311
7 Fort-Hutchinson WA (1995) *Adv Prostaglandin Thromboxane Leukotriene Res* 23, 69–74
8 Gardiner PJ (1989) *Pharmacol Ther* 44, 1–62
9 Von Sprecher A, Beck A, Gerspacher M, Bray MA (1992) *Chimia* 46, 304–311
10 Koch K, Burgess E (1995) *Expert Opin Ther Pat* 5 (2), 127–155
11 Larsen JS, Acosta EP (1993) *Ann Pharmacother* 27 (7-8), 898–903
12 Pauwels RA, Joos GF, Kips JC (1995) *Leukotrienes Ther Target Asthma Allergy* 50 (8), 615–622
13 Chung KF (1995) *Eur Res J* 8 (7), 1203–1213
14 Matassa VG, Maduskuie TP, Shapiro HS et al (1990) *J Med Chem* 33, 1781–1790
15 Nakai H, Konno M, Kosuge S et al (1988) *J Med Chem* 31, 84–91
16 Huang FC, Galemmo RA, Poli GB et al (1991) *J Med Chem* 34, 1704–1707
17 Glass M (1995) *Eur Resp Rev* 5 (26), 120–123
18 Grossman J, Bronsky E, Busse W et al (1995) *J Allergy Clin Immunol* 95 (1), 352
19 Grossman J, Bronsky E, Busse E et al (1995) *Eur Resp J* 8 (suppl 19) 288S
20 Jones G (1977) *In: The Chemistry of Heterocyclic Compounds*. John Wiley and Sons, NY, vol 32, part I, 143
21 Cairns H, Payne AR (1978) *J Heterocycl Chem* 15, 551–553
22 Venturella P, Bellino A, Marino ML, Piozzi F (1990) *Gazz Chim Ital* 100, 678–681
23 Huang FC, Galemmo RA, Johnson WH et al (1990) *J Med Chem* 33, 1194–1200
24 Cassis R, Tapia R, Valderrama JA (1985) *Synth Commun* 15, 125–133
25 Huang X, Chen B (1987) *Synthesis* 480–481
26 Chen B, Huang X, Wang J (1987) *Synthesis* 482–483
27 Lauer WM, Kaslow CE (1949) *Org Synth Coll* III, 580–583
28 Bieber MP (1951) *Comptes Rendus Acad Sci Paris* 233, 655–657
29 Alvarez M, Salas M, Rigat Ll, de Veciana A, Joule JA (1992) *J Chem Soc Perkin Trans* I 351–356
30 Wakatsuka H, Nakai H, Okumoto I (1991) *Jpn Kokai Tokyo Koho* 03 95, 144 [9195,144] (Cl C07C225/22) 19 Apr 1991, appl 89/202, 682, 04 Aug 1989
31 Palomer A, Giolitti A, García ML, Cabré F, Mauleón D, Carganico G (1995) *In: Trends in QSAR and Molecular Modelling '94* (Sanz F, Manaut F, eds) Prous, Barcelona
32 Sprague P (1995) *In: De Novo Design* (Müller K, ed) Escom, Leiden, 1–20
33 Cramer III RD, Patterson DE, Bunce JD (1988) *J Am Chem Soc* 110, 5959–5967
34 Pascual J, Fos E, García ML et al (1994) *Proc XIIIth Int Symp Med Chem* Paris, p 184
35 Greene J, Kahn S, Savoj H, Sprague P, Teig S (1994) *J Chem Inf Comput Sci* 34 (6), 1297–1308
36 Matassa VG, Brown FJ, Bernstein PR et al (1990) *J Med Chem* 33, 2621–2629
37 Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaninathan S, Karplus M (1983) *J Comput Chem* 4, 187–217
38 Smellie AS, Kahn SD, Teig SL (1995) *J Chem Inf Comput Sci* 35 (2), 285–294
39 Smellie AS, Kahn SD, Teig SL (1995) *J Chem Inf Comput Sci* 35 (2), 295–304
40 Smellie AS, Teig SL, Towbin P (1995) *J Comput Chem* 16 (2), 171–187
41 Liu KC, Lu WC, Lee LC (1979) *Taiwan I-Hsueh-Hui Tsa Chih* 31, 80–90
42 Huang X, Chen B (1986) *Synthesis* 967–968
43 Cidda C, Sleiter G (1980) *Gazz Chim Ital* 110, 155–162
44 Denny WA, Atwell GJ, Baguley BC, Cain BF (1979) *J Med Chem* 22, 134–150
45 Crowter AF, Hepworth W, Morley JS (1960) Br Pat 835, 474, Imperial Chemical Industries Ltd
46 Mong S, Wu HL, Clark MA, Stadel JM, Gleason JG, Crooke ST (1984) *Prostaglandins* 28, 805–822
47 Matassa VG, Brown FJ, Bernstein PR et al (1990) *J Med Chem* 33, 2621–2629