Synthesis and Structure−Activity Relationships of Carboxyflavones as Structurally Rigid *CysLT$_1$* (LTD$_4$) Receptor Antagonists

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The synthesis and *CysLT$_1$* receptor affinities of a new series of highly rigid 3′- and 4′-(2-quinolinylmethoxy)- or 3′- and 4′-[2-(2-quinolinyl)ethenyl]-substituted, 6-, 7-, or 8-carboxylated flavones are described. *CysLT$_1$* receptor affinities of the flavones (down to 11 nM) were determined by their ability to displace [^{3}H]LTD$_4$ from its receptor in guinea pig lung membranes. Structure−affinity relationship studies showed that the relative positions of the carboxylic acid and the quinoline moiety were critical for *CysLT$_1$* affinities. While the carboxyl is optimal in the 8 position but tolerated in the 6 position, only the 6- and not the 8-tetrazole has significant activity. The quinoline moiety may be connected to the flavone skeleton by an ethenyl or a methoxy linker, but the substitution position is important for high affinity, especially in the 6-carboxylated flavones. 4′-Substituted 6-carboxyflavones are essentially inactive, whereas the 3′-substituted analogues have submicromolar *CysLT$_1$* affinity. Replacement of the quinoline by other heteroaromates generally leads to decreased affinities, with the phenyl and naphthyl analogues displaying only little or no affinity, while the 7-chloroquinoline analogue is comparable in activity to the quinoline. Flavones having *CysLT$_1$* receptor affinities of 10−30 nM were selected for determination of their inhibitory effects on the LTD$_4$-induced contraction of guinea pig ileum in vitro. The IC$_{50}$ values ranged between 15 and 100 nM. Compound **5d** (8-carboxy-6-chloro-3′-(2-quinolinylmethoxy)flavone, VUF 5087) was selected for further research because of its high potency in the functional assay. This series contains the most rigid *CysLT$_1$* receptor antagonists known to date, and they are useful in the development of a *CysLT$_1$* antagonist model, which is discussed in the companion paper.

Introduction

Asthma, characterized by a chronic inflammation of the airways, affects about 5% of the population of industrialized areas. Asthmatic reactions are mediated by a wide range of endogenous substances, among which cysteinyl leukotrienes (CysLTs) are most prominent. During the last 2 decades CysLTs have been identified as important bronchoconstrictors, and their pharmacological effects mimic the pathological changes seen in asthma both in vitro and in vivo.[1−8] The biological actions of CysLTs are mediated via activation of at least one specific membrane receptor, the *CysLT$_1$* receptor.[9] *CysLT$_1$* receptor activation leads to bronchoconstriction, increased mucus secretion, and bronchial hyperresponsiveness, all characteristic of asthma.

The unravelling of the biosynthetic pathway and the pathological roles of CysLTs in human diseases[1,10] has led to the development of leukotriene biosynthesis inhibitors, e.g., 5-lipoxygenase (5-LO) inhibitors and 5-lipoxygenase-activating protein (FLAP) inhibitors, and *CysLT$_1$* receptor antagonists as potential therapeutic agents.[11,12] Recent studies on such 'antileukotrienes' have demonstrated clinical efficacy in human asthma, and both classes of agents are now considered the most promising antiasthmatic therapeutics.[2,6,13−17]

Originally the development of new *CysLT$_1$* antagonists was mainly inspired by either FPL 55712 (sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropyl]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylate), the first *CysLT$_1$* receptor antagonist,[18] or LTD$_4$ analogues with antagonistic properties.[19−24] Later new lead structures were discovered, leading to the development of a wide range of compounds such as indoles (e.g., ICI 204,-219/Zafirlukast[25−29]), benzamides (e.g., ONO-1078/Pranlukast[30,31]), thiazoles (e.g., Ro 24-5913/[(*E*)-4-[3-[2-(4-cyclobutyl-2-thiazolyl)ethenyl]phenyl]amino]-2,2-diethyl-4-oxobutanoic acid][32,33]), and quinolines (e.g., RG 12553/[5-[7-[[3-(2-quinolinylmethoxy)phenyl]methoxy]-4-oxo-4*H*-1-benzopyran-2-yl]-1*H*-tetrazole][34] and MK-476/Montelukast[35]) as highly potent antagonists at the *CysLT$_1$* receptor (Chart 1).

Structure−activity relationship studies on the different classes of *CysLT$_1$* antagonists have revealed several important structural features for high potency. It is generally agreed that essential structural requirements for *CysLT$_1$* receptor antagonists are (1) a lipophilic anchor, which fits into the lipophilic pocket of the *CysLT$_1$* receptor; (2) a central flat unit mimicking the triene system of LTD$_4$; (3) one or two acidic groups, as

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Chart 1. *CysLT$_1$* Receptor Antagonists from the Quinoline Class

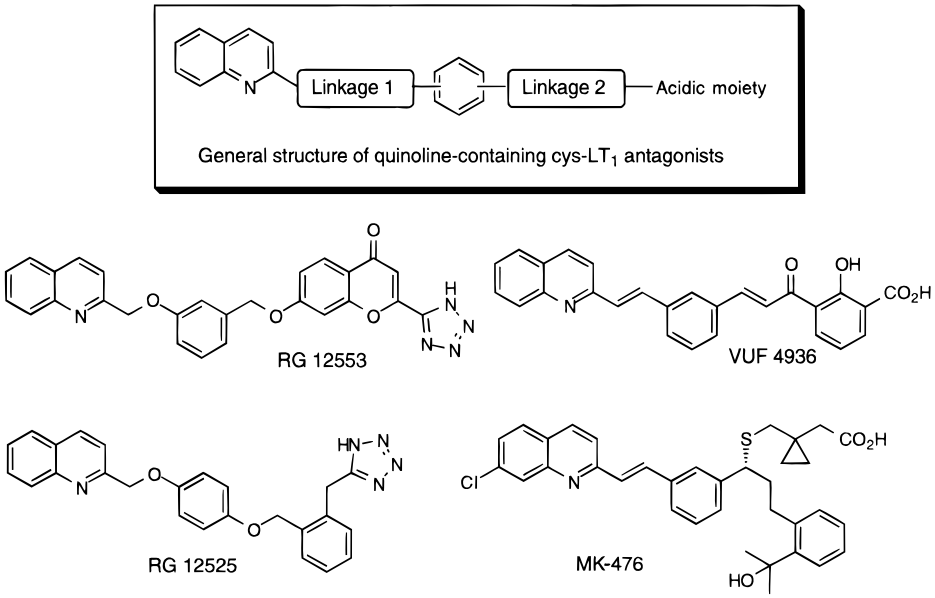
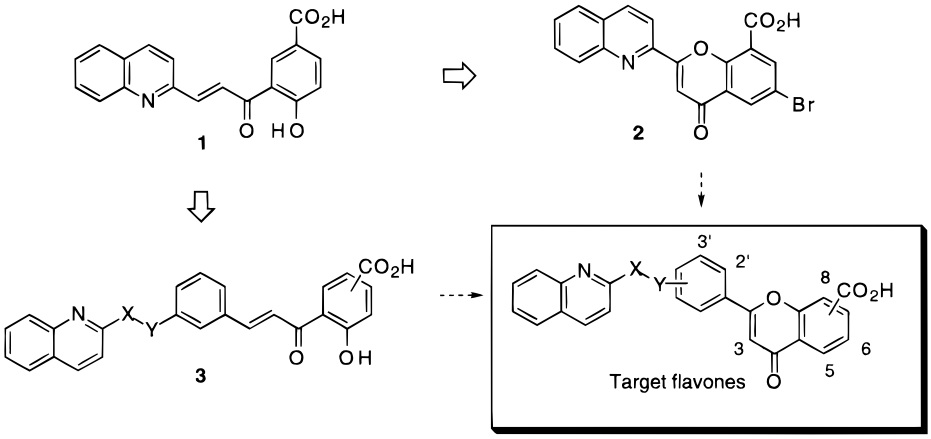


Chart 2. Evolution of the Target Structures



mimics of the peptide units or the C1-carboxylic acid of LTD$_4$; and (4) spacers to connect and preorganize these elements. The lack of any of these characteristic groups may be compensated by stronger interaction in other regions of the receptor.[36] Although several modeling studies on *CysLT$_1$* receptor antagonists have been reported,[37−40] no general model describing the 3D alignment and interaction sites of all classes of ligands has been reported yet, mainly due to the flexibility of the ligands.

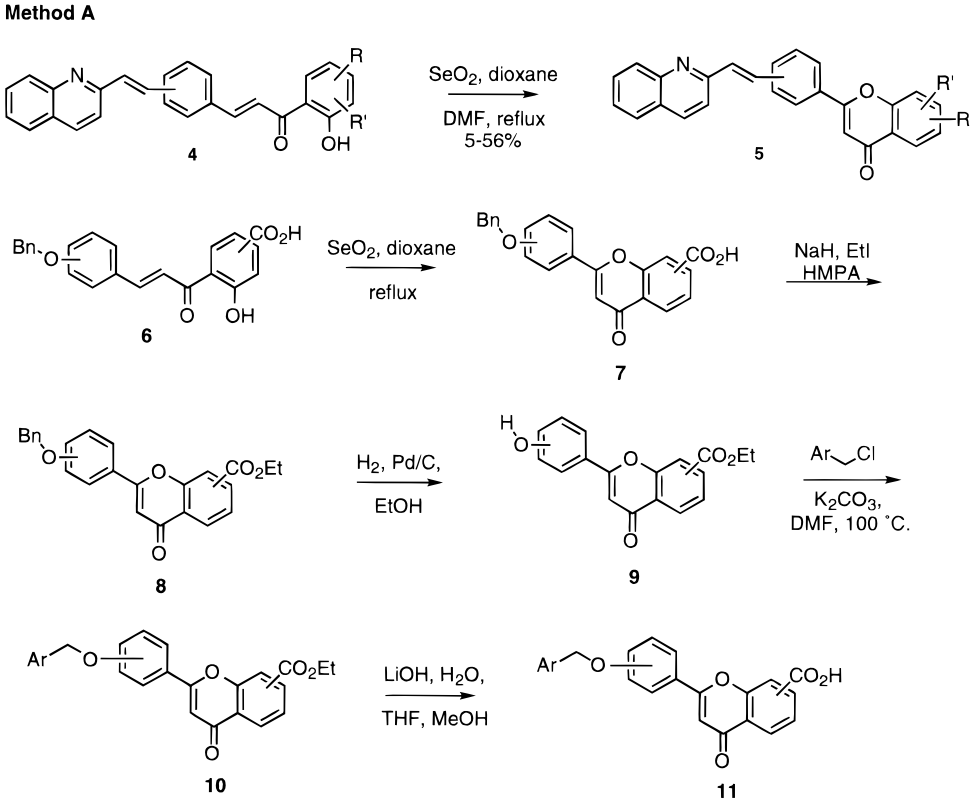
In our search for antiasthmatic drugs, we became interested in the development of *CysLT$_1$* receptor antagonists.[41,42] Our attempts to find new lead structures for *CysLT$_1$* receptor antagonists started with the synthesis of a series of carboxylated flavonoid analogues which led to identification of two new lead structures (**1** and **2**), having weak *CysLT$_1$* affinities (Chart 2).[42] Using **1** as a lead, we have developed a novel series of carboxylated chalcones with potent *CysLT$_1$* antagonistic activities.[43] We now report our efforts in developing rigid *CysLT* antagonists by optimization of the second lead **2**.

As shown in Chart 1, the chalcones of our first series (e.g., VUF 4936) belong to the quinoline-containing *CysLT$_1$* receptor antagonists such as RG 12525 and MK-476 (Montelukast). This class of compounds generally consists of a quinoline moiety connected to a central phenyl ring by a two-atom spacer. The central phenyl is connected to an additional, mostly aromatic group containing an acidic substituent of variable length and nature. The substitution pattern of the central phenyl ring is either meta or para. The conformational freedom of these compounds mainly arises from the flexibility of the spacer groups. Conformational restriction of such quinoline-containing *CysLT$_1$* antagonists can be achieved most effectively by fixation of the spacer groups (Chart 2). The high rigidity of the target flavones (Chart 2) would offer us the possibility to develop a general *CysLT$_1$* antagonist model, in addition to potential antiasthmatic agents.

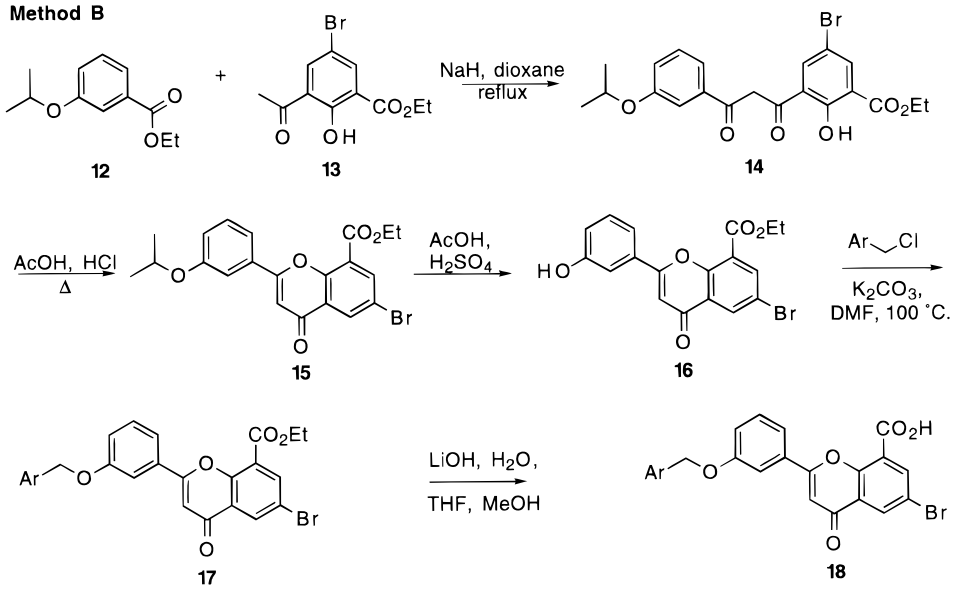
Chemistry

The most convenient method for the preparation of our target flavone derivatives is by a direct conversion of the 2′-hydroxychalcones which we have synthesized previously.[43] Methods available for this conversion involve either dehydrohalogenation[44−46] or ring closure under the influence of oxidants such as SeO_2[47−49] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).[50,51]

Scheme 1. Synthesis of Flavones from 2′-Hydroxychalcones



Scheme 2. Synthesis of Flavones via Cyclodehydration of 1,3-Diphenyl-1,3-propanediones

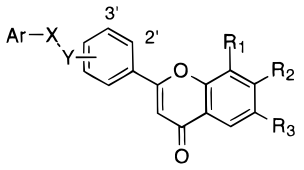


Dehydrohalogenation of chalcones appeared not suitable as a general synthetic strategy for our flavone derivatives, because an unwanted bromination at the flavone 6 or 8 position occurred. Only compound **18g** was prepared via this route. Reaction of 2′-hydroxychalcones with SeO_2 provided a convenient alternative for the conversion of 3- or 4-[2-ethenyl(2-quinolinyl)]-chalcones **4** to their corresponding flavones **5** (method A, Scheme 1) with yields ranging from 5% to 55%.

However the same reaction failed to convert 2-quinolinylmethoxy-substituted chalcones to the corresponding flavones due to the cleavage of the ether bond. Since benzyl ethers were not cleaved under the influence of SeO_2, benzyloxy-substituted chalcones **6** were used as starting materials for hydroxyflavones **9**. Alkylation of **9** and the subsequent hydrolysis of the resulting esters **10** gave access to target flavones **11** (Scheme 1). However, the low overall yield and the difficulty to remove traces of SeO_2 urged us to look for an alternative synthetic route to hydroxyflavones, which could be performed on a multigram scale.

Method B (Scheme 2) was therefore developed for the synthesis of hydroxyflavone **16**. This method, which involves coupling of a hydroxybenzoic ester with a hydroxyacetophenone and subsequent cyclodehydration, has been applied in the synthesis of a wide range of

Table 1. Carboxylated Flavones and Their *CysLT$_1$* Receptor Affinities



no.	Ar	X—Y	position	R_1	R_2	R_3	K_D[a] (nM) (% inhib)[b]	IC_{50}[c] (nM)
5a	2-quinolinyl	C=C	4′	CO_2H	H	H	270 ± 60	
5b	2-quinolinyl	C=C	3′	CO_2H	H	H	17 ± 4	42
5c	2-quinolinyl	C=C	3′	CO_2H	H	Br	17 ± 4	100
5d	2-quinolinyl	C=C	3′	CO_2H	H	Cl	11 ± 3	15
5e	2-quinolinyl	C=C	3′	CO_2H	H	F	127 ± 89	
5f	2-quinolinyl	C=C	3′	CO_2H	H	Me	13 ± 3	28
5g	2-quinolinyl	C=C	3′	CN	H	Cl	(0%)	
5h	2-quinolinyl	C=C	3′	H	CO_2H	H	1730 ± 850	
5i	2-quinolinyl	C=C	4′	H	H	CO_2H	(28%)	
5j	2-quinolinyl	C=C	3′	H	H	CO_2H	408 ± 50	
5k	2-quinolinyl	C=C	3′	H	H	CN	1750 ± 880	
7a	phenyl	CH_2O	3′	CO_2H	H	H	(50%)	
7b	phenyl	CH_2O	4′	CO_2H	H	H	55000 ± 7500	
7c	phenyl	CH_2O	4′	H	H	CO_2H	(23%)	
10a	2-quinolinyl	CH_2O	3′	CO_2Et	H	H	(38%)	
10b	2-quinolinyl	CH_2O	4′	CO_2Et	H	H	(32%)	
11a	2-quinolinyl	CH_2O	3′	CO_2H	H	H	17 ± 3	
11b	2-quinolinyl	CH_2O	4′	CO_2H	H	H	526 ± 88	
11c	2-naphthyl	CH_2O	4′	CO_2H	H	H	(32%)	
11d	2-quinazolinyl	CH_2O	4′	CO_2H	H	H	1100 ± 320	
18a	2-quinolinyl	CH_2O	3′	CO_2H	H	Br	31 ± 9	61
18b	2-naphthyl	CH_2O	3′	CO_2H	H	Br	1130 ± 210	
18c	2-quinazolinyl	CH_2O	3′	CO_2H	H	Br	101 ± 29	
18d	2-benzothiazolyl	CH_2O	3′	CO_2H	H	Br	79 ± 18	
18e	2-(1-methyl)benzimidazolyl	CH_2O	3′	CO_2H	H	Br	210 ± 52	
18f	7-chloro-2-quinolinyl	CH_2O	3′	CO_2H	H	Br	12 ± 3	
18g	2-quinolinyl	CH_2O	4′	CO_2H	H	Br	504 ± 300	
19a	2-quinolinyl	C=C	3′	CN_4H	H	Cl	11000 ± 1900	
19b	2-quinolinyl	C=C	3′	H	H	CN4H	307 + 98	
20	2-quinolinyl	CH_2O	4′	$CONHSO_2Ph$	H	Br	382 ± 49	

[a] The affinity data were obtained from binding assays in guinea pig lung membranes vs [^{3}H]LTD_4. The data are means ± SD of three determinations. [b] In case no K_D could be determined, percent inhibition is determined as the quotient of the maximum binding minus the counting at 10^{-5} M drug concentration and the maximum binding times 100. [c] Determined by evaluation of the inhibitory effect of the drug on LTD_4-induced contraction of guinea pig ileum.

flavones.[52−56] Although in this procedure benzyl and *tert*-butyldimethylsilyl (TBDMS) proved unsuitable as protective groups for the hydroxyl, protection of the hydroxyl as an isopropyl ether did give good results. Thus coupling of isopropoxybenzoate **12** with acetophenone **13** yielded 1,3-propanedione **14** which upon cyclization afforded flavone **15**. Subsequent deprotection and alkylation provided target flavones **18**. Reaction of **12** with the nonbrominated analogue of **13** gave an unidentified mixture of products, probably due to the instability of the latter under the required reaction conditions.

Tetrazolylflavones were prepared from their corresponding nitriles by reaction with sodium azide and ammonium chloride. Phenylsulfonylamides were synthesized by reaction of the carboxylic acid and phenylsulfonylamine in the presence of a carbodiimide and 4-(dimethylamino)pyridine.[26]

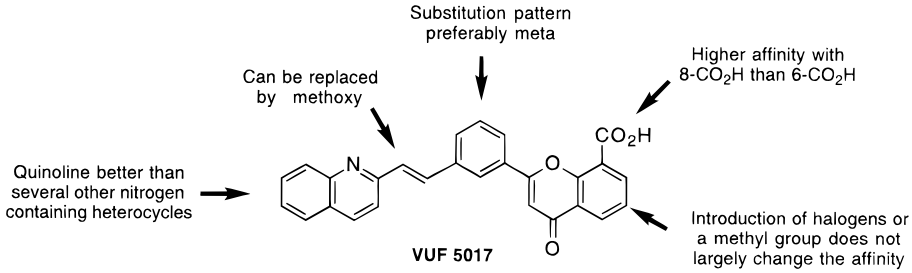
Results and Discussion

CysLT$_1$ receptor affinities of the flavones were determined in vitro by their ability to displace [^{3}H]LTD_4 from its binding site on guinea pig lung membranes (Table 1), and the K_D values of the most potent flavones are approaching 10 nM. Structure−affinity relationship analysis showed that the relative positions of the carboxylic acid and the quinoline moiety seemed critical for the *CysLT$_1$* affinities. Comparison of **5b**,**j** seems to suggest that in the 3′-substituted flavones the carboxylic acid is preferred at the 8 position. In the 8-carboxylated flavones, the quinoline can be attached to both the 3′ and 4′ positions, regardless of the linkers being an ether or ethenyl group. Actually there is no significant difference in the activities of compounds different only in the linking unit. The 4′-substituted flavones are generally 10−20 times less potent than their 3′-substituted analogues (e.g., **5a** vs **5b**).

The position of the quinoline moiety is more critical in the 6-carboxylated flavones. The 4′-substituted flavone **5i** is essentially inactive, whereas the 3′-substituted **5j** has submicromolar *CysLT$_1$* affinity. The activity of **5j** clearly shows that the relative arrangement of the carboxylic group and the heterocycle is important for *CysLT$_1$* activity rather than the specific substitution position of the group.

Replacement of the 8-carboxylic acid by a nonacidic ethyl ester or nitrile abolished the receptor affinity (**10b** vs **11b** and **5g** vs **5d**). Replacement of the carboxylic acid of **18g** by a sulfonylamide gives **20** which has comparable *CysLT$_1$* affinity. Replacement of carboxylic acid by the well-known bioisoster tetrazole gave variable influence on the activity (Table l).

Chart 3. Summarized Structure−Affinity Relationships of Carboxylated Flavones



Introduction of halogens or a methyl group at the 6 position of 8-carboxylated flavones generally did not significantly affect the $CysLT_1$ receptor affinities. There is no significant difference in the affinities between 6-brominated and nonbrominated flavones (**11b** vs **18g** and **5b** vs **5c**). Within the series of **5b**−**f**, halogen or methyl substitution appeared not to affect $CysLT_1$ affinity significantly except for the fluorine-substituted analogue **5e** which is somehow 10-fold less potent. Since the chlorine and bromine analogues display similar affinities, the decreased affinity of the fluorine analogue is unlikely to be caused by electronic effects.

Within the series of **18**, in which the quinoline moiety of **18a** was replaced by other aromatic groups, it appears that the presence of a nitrogen atom in the aromatic group is important for $CysLT_1$ activity with quinoline and 7-chloroquinoline being the groups of choice. The naphthyl and phenyl derivatives (also compare **7a**,**b** vs **11a**,**b** and **11b** vs **11c**) displayed only little or no affinity, whereas quinazoline (**18c**) and 1-methylbenzimidazole (**18e**) derivatives retained reasonable activity.

The relative positions of the quinoline and the acidic moiety are more critical than those previously observed for the carboxylated chalcones.[43] This most likely is due to the increased rigidity of the flavone series. The higher flexibility of the corresponding chalcones allows them to adopt several conformations. The structure−activity relationships of the present flavone series therefore provide crucial information about the bioactive conformation of these $CysLT_1$ receptor antagonists, although NOE difference spectroscopy indicated no preferred geometry for these molecules.

Flavones **5b**−**d**,**f** and **18a**, having $CysLT_1$ receptor affinities of 10−30 nM, were selected for determination of their inhibitory effects against the LTD_4-induced contraction of guinea pig ileum in vitro. The IC_{50} values, which are the drug concentrations at which one-half of the contraction is blocked, are shown in Table 1. The flavones with the best $CysLT_1$ receptor affinity also displayed good in vivo antagonistic potency.

Conclusion

We have described the development of a series of carboxylated flavones, which are the most rigid $CysLT_1$ receptor antagonists known so far. $CysLT_1$ affinities of 8-carboxylated flavones are approaching the nanomolar range and are comparable to those of their chalcone precursors,[43] showing that no affinity was lost upon fixation of the molecular structures. The most important structure−affinity relationships have been summarized in Chart 3. Taking **5b** (VUF 5017) as the template of this series, we conclude that quinoline is the optimal heterocyclic moiety. The connection between the central phenyl ring and the quinoline may be either *trans*-ethene or methoxy; the preferred substitution pattern for the central phenyl ring is meta. Para substitution generally leads to a 10-fold decreased affinity. The position of the carboxylic acid moiety can be either 6, 7, or 8, with the 8-carboxylated flavone having the highest $CysLT_1$ affinity. Introduction of halogens or a methyl group in the flavone 6 position does not severely affect the $CysLT_1$ affinity.

A selection of flavone derivatives has been shown to antagonize the LTD_4-induced contraction of guinea pig ileum in a dose-dependent manner. With the availability of highly rigid $CysLT_1$ antagonists such as **5b**, we are able to develop a more reliable $CysLT_1$ antagonist model.[57]

Experimental Section

A. Pharmacology. Radioligand Displacement Studies with [^{3}H]LTD$_4$. The method is very similar to that described previously.[41] Briefly, a mixture of a total volume of 0.3 mL containing 0.2 nM [^{3}H]LTD_4, guinea pig lung membrane fractions (±170 μg/mL), and the testing compound in a 10 mM piperazine-*N*,*N*′-bis(2-ethanesulfonic) acid buffer (pH 7.5) was incubated at 22 °C for 30 min. The piperazine-*N*,*N*′-bis(2-ethanesulfonic) acid buffer contains 10 mM $CaCl_2$, 10 mM $MgCl_2$, 50 mM NaCl, 2 mM cysteine, and 2 mM glycine. The reaction was terminated by the addition of 5 mL of ice-cold Tris-HCl/NaCl buffer (10 mM/100 mM, pH 7.5). The mixture was immediately filtered under vacuum (Whatman GF/C filters), and the filters were washed once with 20 mL of ice-cold buffer. The retained radioactivity was determined by a liquid scintillation counter. In the saturation experiment, 2 μM LTD_4 was used to define the nonspecific binding. A single, saturable binding site with B_{max} = 988 fmol/mg of protein was found from saturation experiments. The K_D of [^{3}H]LTD_4 was established to be 2.16×10^{-10} M, and no cooperativity was detected when the data were analyzed by Hill plots (slope = 0.99).

In Vitro Inhibition of LTD$_4$-Induced Contraction of Guinea Pig Ileum. The method is similar to that described previously.[41] Male guinea pigs were killed by a sharp blow to the head, and ileum sections were removed immediately. Each segment (2 cm) was tied to a holder and attached to a transducer by means of a thread, leaving the lumen open. The ilea were then transferred to 20-mL organ baths maintained at 29 °C and continuously aerated with 95% O_2 and 5% CO_2 and washed with Tyrode's solution containing atropine (10^{-6} M) and pyrilamine (10^{-6} M). The contraction of ileum was measured isotonically (resting tension was 1.0 g). The test compounds were dissolved in dimethyl sulfoxide, and after 30-min preincubation of the test compounds at different concentrations of (10^{-5} M−3.0×10^{-9} M), the contraction induced by 10^{-8} M LTD_4 was obtained. Indomethacin (10^{-6} M) was added in the organ baths 10 min before the addition of LTD_4. IC_{50} values were calculated from the percent inhibition at the different drug concentrations.

B. Chemistry. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H, 200.13 MHz; ^{13}C, 50.32

MHz) or a Bruker 400 MSL spectrometer (^{1}H, 400.13 MHz; ^{13}C, 100.63 MHz). ^{1}H NMR chemical shifts (δ) are reported in ppm relative to $CHCl_3$ ($\delta = 7.25$ ppm) or DMSO-d_5 ($\delta = 2.5$ ppm). ^{13}C NMR chemical shifts (δ) are reported in ppm relative to $CDCl_3$ ($\delta = 77.0$ ppm) or DMSO-d_6 ($\delta = 39.5$ ppm). Coupling constants are given in Hz. 2D NMR (H−H and C−H COSY) techniques were frequently used to support interpretation of 1D spectra. NOE difference spectra were recorded on the Bruker 400 MSL spectrometer. The multiplicity of the carbon signals was determined by DEPT or APT spectra or by a combination of a normal decoupled carbon spectrum in combination with a CH correlation. The symbols used are (p) for primary, (s) for secondary, (t) for tertiary, and (q) for quaternary carbon signals.

FAB (HRMS) was registered on a Finnigan MAT 90 spectrometer equipped with a WATV Cs ion gun, operated at a beam current of approximately 2 μA at 25 kV. High-resolution mass spectra were recorded on a Finnigan MAT-90. Melting points were measured on a Mettler FP-5 + FP-52 apparatus equipped with a microscope and are uncorrected.

Starting materials were commercially available; chalcones **4** and **6**[43] and acetophenone **13**[42] were prepared according to literature procedures. All end products had elemental analysis within 0.4% of theoretical value unless indicated otherwise. However, compounds obtained in too small quantities to perform the elemental analysis or having an elemental analysis slightly outside of this range were found to be pure by both spectroscopic and chromatographic criteria.

Method A. General Procedure for the Preparation of Flavones 5a−k and 6a,b as Exemplified by the Preparation of Flavone 5a. A mixture of 3′-carboxy-2′-hydroxy-4-[2-(2-quinolinyl)ethenyl]chalcone (2.1 g, 5 mmol) and selenium dioxide (1.22 g, 11 mmol) in 50 mL of dioxane was refluxed for 8 h. The reaction mixture was filtered while was hot. The crude product precipitated from the mother liquor upon cooling and was collected by filtration. Two recrystallizations from DMF afforded **5a** as a pure crystalline solid, yield 44%, mp 268.1−270.0 °C. ^{1}H NMR (400 MHz, 348 K, DMSO): δ 7.16 (s, 1H, H3), 7.57 (t, 2H, $^3J = 7.6$ Hz, H6, H6-quinoline), 7.65 (d, 1H, $^3J = 16.4$ Hz, Hα), 7.76 (ddd, 1H, $^3J = 8.3$ Hz, $^3J = 6.9$ Hz, $^4J = 1.3$ Hz, H7-quinoline), 7.88 (d, 1H, $^3J = 8.5$ Hz, H3-quinoline), 7.90 (d, 1H, $^3J = 16.4$ Hz, Hβ), 7.92−7.96 (m, 3H, H5-quinoline, H2′, H6′), 8.01 (d, 1H, $^3J = 8.3$ Hz, H8-quinoline), 8.25−8.29 (m, 4H, H3′, H5′, H5, H7), 8.36 (d, 1H, $^3J = 8.5$ Hz, H4-quinoline). ^{13}C NMR (100 MHz, 348 K, DMSO): δ 106.24 (t), 119.78 (t), 121.56 (q), 123.89 (q), 124.42 (t), 125.97 (t), 126.64 (t), 126.79 (q), 127.36 (t), 127.38 (t), 128.32 (t), 128.70 (t), 129.46 (t), 130.35 (q), 130.63 (t), 132.52 (t), 135.63 (t), 136.18 (t), 139.45 (q), 147.29 (q), 153.44 (q), 154.80 (q), 161.80 (q), 164.75 (q), 176.07 (q). Anal. ($C_{27}H_{17}NO_4 \cdot 0.9H_2O$) C, H, N.

8-Carboxy-3′-[2-(2-quinolinyl)ethenyl]flavone (5b). The title compound was prepared by the method used for compound **5a** above, yield 52%, mp >300 °C. ^{1}H NMR (400 MHz, 368 K, DMSO): δ 7.20 (s, 1H, H3), 7.59 (t, 1H, $^3J = 7.7$ Hz, H6), 7.62−7.66 (m, 1H, H6-quinoline), 7.67 (t, 1H, $^3J = 7.7$ Hz, H5′), 7.70 (d, 1H, $^3J = 16.3$ Hz, PhCH=CHquinoline), 7.81−7.86 (m, 1H, H7-quinoline), 7.95 (d, 1H, $^3J = 7.7$ Hz, H4′ or H6′), 7.97−8.00 (m, 1H, H4′ or H6′), 7.98 (d, 1H, $^3J = 8.6$ Hz, H3-quinoline), 8.00 (d, 1H, $^3J = 16.3$ Hz, PhCH=CH-quinoline), 8.12 (d, 1H, $^3J = 8.5$ Hz, H5-quinoline), 8.17−8.20 (m, 1H, H8-quinoline), 8.29 (m, 1H, H5/7), 8.31 (m, 1H, H5/7), 8.50 (d, 1H, $^3J = 8.6$ Hz, H4-quinoline), 8.57−8.58 (br s, 1H, H2,). ^{13}C NMR (100 MHz, 368 K, DMSO): δ 106.64 (t, C3), 119.65 (t, C3-quinoline), 121.70 (q), 123.93 (q), 124.40 (t, C6), 124.88 (t, C2′), 126.35 (t, C6-quinoline), 126.42 (t, C8-quinoline), 126.76 (t, C5-quinoline), 126.81 (q), 127.50 (t, C4′ or C6′), 128.01 (t, C-olefin), 128.66 (t, C5 or C7), 129.23 (t, C5′), 130.19 (t, C7-quinoline), 130.29 (t, C4′ or C6′), 131.47 (q), 134.60 (t, C-olefin), 135.60 (t, C5 or C7), 136.65 (q), 137.68 (t, C4-quinoline), 145.50 (q), 153.49 (q), 154.34 (q), 161.94 (q), 164.67 (q), 176.10 (q). Anal. ($C_{27}H_{17}NO_4 \cdot 1.3HCl$) C, H, N.

8-Carboxy-6-bromo-3′-[2-(2-quinolinyl)ethenyl]flavone (5c). The title compound was prepared by the method used for compound **5a** above, yield 56%, mp >300 °C. ^{1}H NMR (400 MHz, 328 K, DMSO): δ 7.31 (s, 1H, H3), 7.55−7.59 (m, 1H, H6-quinoline), 7.61−7.66 (m, 1H, H5′), 7.65 (d, 1H, $^3J = 16$ Hz, PhCH=CH-quinoline), 7.75−7.79 (m, 1H, H7-quinoline), 7.85 (d, 1H, $^3J = 8.6$ Hz, H3-quinoline), 7.88 (d, 1H, $^3J = 16$ Hz, PhCH=CH-quinoline), 7.93−7.96 (m, 2H, H4′, H5-quinoline), 8.01 (d, 1H, $^3J = 8.6$ Hz, H8-quinoline), 8.15 (d, 1H, $^3J = 7.8$ Hz, H6′), 8.31 (d, 1H, $^4J = 2.6$ Hz, H5 or H7), 8.34 (d, 1H, $^4J = 2.6$ Hz, H5 or H7), 8.37 (d, 1H, $^3J = 8.6$ Hz, H4-quinoline), 8.57 (m, 1H, H2′). ^{13}C NMR (100 MHz, 328 K, DMSO): δ 106.72 (t), 116.69 (q), 119.90 (t), 124.83 (t), 125.68 (q), 125.97 (t), 126.20 (t), 126.87 (q), 127.47 (t), 128.43 (t), 129.32 (t), 129.51 (t), 129.90 (t), 130.58 (t), 130.67 (t), 131.17 (q), 132.74 (t), 136.22 (t), 137.03 (q), 137.76 (t), 147.44 (q), 152.59 (q), 155.01 (q), 162.37 (q), 163.60 (q), 175.08 (q), 199.89 (q). Anal. ($C_{27}H_{17}NO_4 \cdot 1.3HCl$) C, H, N; Br: calcd, 15.36; found, 14.90.

8-Carboxy-6-chloro-3′-[2-(2-quinolinyl)ethenyl]flavone (5d). The title compound was prepared by the method used for compound **5a** above, yield 8%, mp >300 °C. ^{1}H NMR (400 MHz, 300 K, DMSO): δ 7.35 (s, 1H, H3), 7.56−7.60 (m, 1H, H6-quinoline), 7.63 (t, 1H, $^3J = 7.8$ Hz, H5′), 7.67 (d, 1H, $^3J = 16.3$ Hz, PhCH=CH-quinoline), 7.75−7.79 (m, 1H, H7-quinoline), 7.87 (d, 1H, $^3J = 8.5$ Hz, H3-quinoline), 7.89 (d, 1H, $^3J = 16.3$ Hz, PhCH=CH-quinoline), 7.94−7.97 (m, 2H, H5-quinoline, H4′), 8.00 (d, 1H, $^3J = 8.3$ Hz, H8-quinoline), 8.13 (d, 1H, $^4J = 2.7$ Hz, H5 or H7), 8.17 (d, 1H, $^3J = 7.9$ Hz, H6′), 8.20 (d, 1H, $^4J = 2.7$ Hz, H5 or H7), 8.37 (d, 1H, $^3J = 8.5$ Hz, H4-quinoline), 8.61 (s, 1H, H2′). ^{13}C NMR (100 MHz, 335 K, DMSO): δ 106.56 (t, C3), 119.91 (t, C3-quinoline), 124.88 (t, C2′), 125.32 (q), 125.61 (q), 126.00 (t, C6-quinoline), 126.26 (t, C4′ or C6′), 126.90 (t, C5 or C7), 127.49 (t, C4′ or C6′), 128.44 (t, C8-quinoline), 129.04 (q), 129.35 (t, C5′), 129.54 (t, C7-quinoline), 129.91 (t, C-olefin), 130.56 (C5-quinoline), 131.25 (q), 132.80 (t, C-olefin), 134.82 (t, C5 or C7), 136.25 (C4-quinoline), 137.04 (q), 147.45 (q), 152.10 (q), 155.04 (q), 162.43 (q), 163.86 (q), 175.37 (q), 199.84 (q). Anal. ($C_{27}H_{16}ClNO_4 \cdot 1.1H_2O$) C, H, N, Cl.

8-Carboxy-6-fluoro-3′-[2-(2-quinolinyl)ethenyl]flavone (5e). The title compound was prepared by the method used for compound **5a** above, yield 30%, mp > 300 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.28 (s, 1H, H3), 7.56−7.59 (m, 1H, H6-quinoline), 7.64 (t, 1H, $^3J = 7.8$ Hz, H5′), 7.66 (d, 1H, $^3J = 16.4$ Hz, H-olefin), 7.75−7.79 (m, 1H, H7-quinoline), 7.85 (d, 1H, $^3J = 8.5$ Hz, H3-quinoline), 7.89 (d, 1H, $^3J = 16.4$ Hz, H-olefin), 7.94−7.97 (m, 3H, H5/7, H5-quinoline, H4′), 8.02 (d, 1H, $^3J = 8.4$ Hz, H8-quinoline), 8.09 (dd, 1H, $^3J = 8.5$ Hz, $^4J = 3.2$ Hz, H5/7), 8.16 (d, 1H, $^3J = 7.8$ Hz, H6′), 8.37 (d, 1H, $J = 8.5$ Hz, H4-quinoline), 8.57 (br s, 1H, H2′). ^{13}C NMR (100 MHz, 335 K, DMSO): δ 106.04 (t, C3), 113.63 (t, C5/7, $^2J_{CF} = 23.4$ Hz), 119.90 (t, C3-quinoline), 123.20 (t, C5/7, $^2J_{CF} = 26.8$ Hz), 124.25 (q, $^3J_{CF} = 7.0$ Hz), 124.82 (t, C2′), 125.57 (q, $^3J_{CF} = 7.0$ Hz), 125.97 (t, C6-quinoline), 126.18 (t, C6′), 126.88 (q), 127.47 (t, C5-quinoline), 128.40 (t, C8-quinoline), 129.31 (t, C5′), 129.52 (t, C7-quinoline), 129.86 (t, C-olefin), 130.52 (t, C4′), 131.26 (q), 132.79 (t, C-olefin), 136.25 (t, C4-quinoline), 137.03 (q), 147.40 (q), 150.08 (q), 155.00 (q), 157.64 (q, $^1J_{CF} = 247.8$ Hz, C6), 162.37 (q), 163.73 (q), 175.56 (q). Anal. ($C_{27}H_{16}FNO_4 \cdot 0.7HCl$) C, H, N, F.

8-Carboxy-6-methyl-3′-[2-(2-quinolinyl)ethenyl]flavone (5f). The title compound was prepared by the method used for compound **5a** above, yield 35%, mp >300 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 2.48 (s, 3H, $ArCH_3$), 7.21 (s, 1H, H3), 7.55−7.59 (m, 1H, H6-quinoline), 7.63 (t, 1H, $J = 7.5$ Hz, H5′), 7.64 (d, 1H, $^3J = 15.6$ Hz, H-olefin), 7.74−7.78 (m, 1H, H7-quinoline), 7.86 (d, 1H, $^3J = 8.5$ Hz, H3-quinoline), 7.89 (d, 1H, $^3J = 15.6$ Hz, H-olefin), 7.92−7.96 (m, 2H, H5-quinoline, H4′), 8.02 (d, 1H, $^3J = 8.4$ Hz, H8-quinoline), 8.06 (d, 1H, $^4J = 2.2$ Hz, H5/7), 8.12 (d, 1H, $^4J = 2.2$ Hz, H5/7), 8.15 (d, 1H, $^3J = 8.2$ Hz, H6′), 8.36 (d, 1H, $^3J = 8.5$ Hz, H4-quinoline), 8.56 (s, 1H, H2′). ^{13}C NMR (50 MHz, DMSO): δ 20.27 (p), 106.73 (t), 120.28 (t), 121.38 (q), 124.03 (q), 124.93 (t), 126.35 (t), 126.42 (t), 127.14 (q), 127.88 (t), 128.67 (t),

128.75 (t), 129.63 (t), 129.89 (t), 129.95 (t), 130.81 (t), 131.67 (q), 133.11 (t), 134.52 (q), 136.63 (t), 137.11 (q), 137.23 (t), 147.62 (q), 152.19 (q), 155.32 (q), 162.04 (q), 165.33 (q), 176.69 (t). Anal. ($C_{28}H_{19}NO_4 \cdot 1.9HCl$) C, H; N: calcd, 2.79; found, 3.33.

6-Chloro-8-cyano-3′-[2-(2-quinolinyl)ethenyl]flavone (5g). The title compound was prepared by the method used for compound **5a** above, yield 53%, mp 281.2−281.6 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.37 (s, 1H, H3), 7.56−7.60 (m, 1H, H6-quinoline), 7.69 (d, 1H, ^3J = 16.5 Hz, H-olefin), 7.70−7.74 (m, 1H, H5′), 7.75−7.79 (m, 1H, H7-quinoline), 7.85 (d, 1H, ^3J = 8.6 Hz, H3-quinoline), 7.90−8.07 (m, 5H, H-olefin, H4′, H6′, H5-quinoline, H8-quinoline), 8.27 (d, 1H, ^4J = 1.9 Hz, H5/7), 8.38 (d, 1H, ^3J = 8.5 Hz, H4-quinoline), 8.49 (s, 1H, H2′), 8.54 (d, 1H, ^4J = 1.9 Hz, H5/7). Anal. ($C_{27}H_{15}ClN_2O_2 \cdot 0.3H_2O$) C, H, N, Cl.

7-Carboxy-3′-[2-(2-quinolinyl)ethenyl]flavone (5h). The title compound was prepared by the method used for compound **5a** above, yield 35%, mp >300 °C. ^{1}H NMR (200 MHz, DMSO): δ 7.30 (s, 1H, H3), 7.55−7.61 (m, 1H, H6-quinoline), 7.65 (t, 1H, ^3J = 7.8 Hz, H5′), 7.76 (d, 1H, ^3J = 16.3 Hz, Ha), 7.75−7.82 (m, 1H, H7-quinoline), 7.92 (d, 1H, ^3J = 9.3 Hz, H3-quinoline), 7.96−8.09 (m, 5H, H4′, H6, H5-quinoline, H8-quinoline, Hb), 8.13−8.17 (m, 1H, H6′), 8.16 (d, 1H, ^3J = 8.2 Hz, H5), 8.42 (d, 1H, ^3J = 8.4 Hz, H4-quinoline), 8.43 (d, 1H, ^4J = 1.1 Hz, H8), 8.57 (br s, 1H, H2′). ^{13}C NMR (50 MHz, DMSO): δ 107.32 (t), 119.84 (t), 119.90 (t), 124.94 (t), 125.14 (t), 125.23 (t), 125.76 (q), 126.19 (t), 126.34 (t), 126.88 (q), 127.65 (t), 128.18 (t), 129.46 (t), 129.60 (t), 129.83 (t), 130.48 (t), 131.31 (q), 133.11 (t), 135.60 (q), 136.65 (t), 136.97 (q), 155.05 (q), 155.15 (q), 162.65 (q), 165.81 (q), 176.60 (q).

6-Carboxy-4′-[2-(2-quinolinyl)ethenyl]flavone (5i). The title compound was prepared by the method used for compound **5a** above, yield 28%, mp >300 °C. ^{1}H NMR (400 MHz, 330 K, DMSO): δ 7.10 (s, 1H, H3), 7.55−7.59 (m, 1H, H6-quinoline), 7.64 (d, 1H, ^3J = 16.4 Hz, PhCH═CH-quinoline), 7.74−7.78 (m, 1H, H7-quinoline), 7.86 (d, 1H, ^3J = 8.7 Hz, H8), 7.89 (d, 1H, ^3J = 8.5 Hz, H3-quinoline), 7.90 (d, 1H, ^3J = 16.4 Hz, PhCH═CH-quinoline), 7.90−7.93 (m, 1H, H5-quinoline), 7.93 (d, 2H, ^3J = 8.6 Hz, H3′, H5′), 8.01 (d, 1H, ^3J = 8.5 Hz, H8-quinoline), 8.17 (d, 2H, ^3J = 8.6 Hz, H2′, H6′), 8.32 (dd, 1H, ^3J = 8.7 Hz, ^4J = 2.1 Hz, H7), 8.36 (d, 1H, ^3J = 8.5 Hz, H4-quinoline), 8.60 (d, 1H, ^4J = 2.1 Hz, H5). ^{13}C NMR (100 MHz, 328 K, DMSO): δ 106.96 (t), 118.46 (q), 118.57 (t), 119.87 (t), 122.81 (q), 126.09 (t), 126.19 (t), 126.67 (t), 126.93 (q), 127.48 (t), 127.54 (t), 128.51 (t), 129.56 (t), 130.39 (q), 130.84 (t), 132.57 (t), 134.14 (t), 136.26 (t), 139.60 (q), 147.48 (q), 154.94 (q), 162.01 (q), 162.19 (q), 166.03 (q), 176.46 (q). Anal. ($C_{27}H_{17}NO_4 \cdot Se(OH)_2$) C; H: calcd, 4.23; found, 4.69. N: calcd, 3.09; found, 5.36.

6-Carboxy-3′-[2-(2-quinolinyl)ethenyl]flavone (5j). The title compound was prepared by the method used for compound **5a** above, yield 5%, mp 275−277 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.21 (s, 1H, H3), 7.56−7.60 (m, 1H, H6-quinoline), 7.64−7.68 (m, 1H, H5′), 7.67 (d, 1H, ^3J = 7.8 Hz, H8), 7.70 (d, 1H, ^3J = 16.5 Hz, H-olefin), 7.75−7.79 (m, 1H, H7-quinoline), 7.88 (d, 1H, ^3J = 8.3 Hz, H3-quinoline), 7.93−7.98 (m, 3H, H4′, H6′, H-olefin), 8.02 (d, 1H, ^3J = 8.5 Hz, H5-quinoline), 8.08 (d, 1H, ^3J = 7.7 Hz, H8-quinoline), 8.33−8.35 (m, 1H, H7), 8.37 (d, 1H, ^3J = 8.7 Hz, H4-quinoline), 8.49 (br s, 1H, H2′), 8.64 (br s, 1H, H5). ^{13}C NMR (100 MHz, 335 K, DMSO): δ 107.39 (t), 118.86 (t), 119.78 (t), 122.85 (q), 124.84 (t), 125.96 (t), 126.07 (t), 126.29 (t), 126.87 (q), 2127.46 (t), 128.23 (q), 128.43 (t), 129.36 (t), 129.51 (t), 130.05 (t), 130.21 (t), 131.39 (t), 132.73 (q), 134.06 (t), 136.22 (t), 137.11 (q), 147.46 (q), 155.08 (q), 157.77 (q), 162.43 (q), 165.94 (q), 176.47 (q). Anal. ($C_{27}H_{17}NO_4 \cdot SeO_2$) H, N; C: calcd, 61.14; found, 64.77.

6-Cyano-3′-[2-(2-quinolinyl)ethenyl]flavone (5k). The title compound was prepared by the method used for compound **5a** above, yield 39%, mp 271.8−272.9 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.24 (s, 1H, H3), 7.56−7.60 (m, 1H, H6-quinoline), 7.65 (t, 1H, ^3J = 7.8 Hz, H5′), 7.68 (d, 1H, ^3J = 16.3 Hz, H-olefin), 7.75−7.79 (m, 1H, H7-quinoline), 7.87 (d, 1H, ^3J = 8.6 Hz, H3-quinoline), 7.92 (d, 1H, ^3J = 16.4 Hz, H-olefin), 7.94−7.96 (m, 2H, H4, H6), 8.01 (d, 1H, ^3J = 8.3 Hz, H5-quinoline), 8.03 (d, 1H, ^3J = 8.7 Hz, H8), 8.06 (d, 1H, ^3J = 7.9 Hz, H8-quinoline), 8.21 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.9 Hz, H7), 8.38 (d, 1H, ^3J = 8.6 Hz, H4-quinoline), 8.42 (d, 1H, ^4J = 1.9 Hz, H5), 8.46 (s, 1H, H2′). ^{13}C NMR (100 MHz, 335 K, DMSO): δ 107.59, 108.23, 117.39, 119.73, 120.28, 123.54, 124.69, 126.19, 126.85, 127.49, 128.07, 129.34, 129.68, 129.99, 130.41, 131.05, 133.02, 136.41, 136.55, 137.03, 147.03, 154.89, 157.49, 162.62, 175.38. Anal. ($C_{27}H_{16}N_2O_2 \cdot 0.7H_2O$) C, H, N.

3′-(Benzyloxy)-8-carboxyflavone (7a): yield 50%, mp 244.8−246.8 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.20 (s, 2H, $PhCH_2O$), 7.22 (s, 1H, H3), 7.24−7.26 (m, 1H, H4′), 7.44−7.61 (m, 7H, $PhCH_2O$, H6, H5′), 7.82 (d, 1H, ^3J = 7.8 Hz, H6′), 7.95 (s, 1H, H2′), 8.26 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.7 Hz, H5 or H7), 8.30 (dd, 1H, ^3J = 7.3 Hz, ^4J = 1.7 Hz, H5 or H7). ^{13}C NMR (50 MHz, DMSO): δ 69.24 (s), 106.49 (t), 111.90 (t), 118.63 (t), 118.78 (t), 121.33 (q), 123.95 (q), 124.63 (t), 127.77 (t), 127.87 (t), 128.22 (t), 129.10 (t), 129.97 (t), 132.02 (q), 136.18 (t), 136.44 (q), 153.58 (q), 158.55 (q), 161.92 (q), 165.09 (q), 176.42 (q). Anal. ($C_{27}H_{16}O_5 \cdot 0.5DMF$) H, N; C: calcd, 72.21; found, 71.61.

4′-(Benzyloxy)-8-carboxyflavone (7b): yield 80%, mp 203.2−209.1 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.22 (s, 2H, $ArCH_2O$), 7.06 (s, 1H, H3), 7.19 (d, 2H, ^3J = 8.9 Hz, H3′, H5′), 7.36−7.54 (m, 6H, H6, Ph), 8.17 (d, 2H, ^3J = 8.9 Hz, H2′, H6′), 8.21−8.27 (m, 2H, H5, H7), 13.50 (br s, 1H, CO_2H). ^{13}C NMR (50 MHz, DMSO): δ 69.28 (s), 104.83 (t), 115.10 (q), 121.35 (q), 122,98 (q), 123.89 (q), 124.48 (t), 127.60 (t), 127.78 (t), 128.20 (t), 128.25 (t), 128.95 (t), 135.79 (t), 136.25 (q), 153.52 (q), 161.14 (q), 162.36 (q), 164.99 (q), 176.14 (q).

6-Chloro-3′-[2-(2-quinolinyl)ethenyl]-8-(5-tetrazolyl)-flavone (19a). A mixture of cyanoflavone **5g** (0.45 g, 1 mmol), sodium azide (0.32 g, 5 mmol), and ammonium chloride (0.27 g, 5 mmol) in 30 mL of DMF was heated at 100 °C for 3 days. The reaction mixture was poured into water and acidified to pH 5. The precipitate was collected by filtration, dried, and recrystallized from ethanol/DMF, yield 9%, mp >300 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.37 (s, H, H3), 7.58−7.65 (m, 3H, H6-quinoline, H5′, H-olefin), 7.76−7.80 (m, 1H, H7-quinoline), 7.87 (d, 1 H, ^3J = 8 Hz, H3-quinoline), 7.92−8.05 (m, 5H, H4′, H6′, H-olefin, H5-quinoline, H8-quinoline), 8.25 (d, 1H, ^4J = 2.4 Hz, H5), 8.41 (s, 1H, H2′), 8.44 (d, 1H, ^4J = 2.3 Hz, H7), 8.47 (d, 1H, ^3J = 8.5 Hz, H4-quinoline), 9.54 (s, 1H, CN_4H). ^{13}C NMR (50 MHz, DMSO): δ 106.08 (t), 122.25 (t), 122.36 (t), 125.04 (t), 125.31 (q), 125.52 (q), 126.19 (t), 126.61 (t), 127.33 (q), 127.42 (t), 127.93 (t), 128.74 (t), 129.55 (q), 129.65 (t), 129.89 (t), 131.42 (q), 132.11 (t), 132.24 (t), 132.53 (t), 136.73 (t), 137.19 (q), 147.68 (q), 150.59 (q), 155.37 (q), 162.72 (q), 173.22 (q), 176.49 (q). MS: *m*/*z* 477 [M$^{\bullet-}$] for ^{35}Cl, 479 [M$^{\bullet-}$] for ^{37}Cl.

3′-[2-(2-Quinolinyl)ethenyl]-6-(5-tetrazolyl)flavone (19b). This compound was prepared in a similar way from the corresponding cyano precursor as described for **19a**, yield 10%, mp >300 °C. ^{1}H NMR (400 MHz, 335 K, DMSO): δ 7.20 (s, 1H, H3), 7.66−7.71 (m, 2H, H5′, H6-quinoline), 7.80 (d, 1H, ^3J = 16.2 Hz, H-olefin), 7.86−7.90 (m, 1H, H7-quinoline), 7.96 (d, 1H, ^3J = 8 Hz, H3-quinoline), 8.05−8.18 (m, 6H, H-olefin, H4′, H6′, H8, H5-quinoline, H8-quinoline), 8.48 (s, 1H, H2), 8.48−8.51 (m, 1H, H4-quinoline), 8.60 (d, 1H, ^3J = 8.0 Hz, H7), 8.76 (s, 1H, H5). ^{13}C NMR (50 MHz, DMSO): δ 107.24 (t), 118.87 (t), 120.21 (t), 120.84 (t), 123.54 (q), 125.05 (t), 126.39 (t), 127.17 (q), 127.91 (t), 128.72 (t), 129.76 (t), 129.99 (t), 130.11 (q), 130.16 (t), 130.46 (t), 131.67 (t), 131.90 (t), 132.01 (q), 133.16 (t), 136.70 (t), 137.29 (q), 147.69 (q), 154.97 (q), 155.46 (q), 159.73 (q), 162.20 (q), 177.44 (q). MS: *m*/*z* 443 [M$^{\bullet-}$].

8-(Ethoxycarbonyl)-3′-[(2-quinolinyl)methoxy]flavone (10a). To a solution of 3′-(benzyloxy)flavone-8-carboxylic acid (1.86 g, 5 mmol) in 25 mL of HMPA was added 0.13 g (5.5 mmol) of NaH. The mixture was stirred at room temperature for 30 min, and ethyl iodide (1.56 g, 10 mmol) was then added. The reaction mixture was stirred for another 2 h at room temperature. The reaction mixture was poured into

water and extracted with ethyl acetate. The combined organic layers were washed with water and brine and dried over Na_2SO_4. Removal of the solvent and subsequent recrystallization from ethanol yielded 3′-(benzyloxy)-8-(ethoxycarbonyl)flavone as a crystalline product, yield 47%, mp 121.0−122.1 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.43 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 5.12 (s, 2H, CH_2O), 6.81 (s, 1H, H3), 7.09 (dd, 1H, ^3J = 8.3 Hz, ^4J = 2.5 Hz, H4′), 7.27−7.44 (m, 7H, H5′, H6, Ph), 7.59−7.63 (m, 1H, H6′), 7.70−7.71 (br s, 1H, H2′), 8.26 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.8 Hz, H5/7), 8.37 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.8 Hz, H5/7). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.32 (p), 61.68 (s), 70.10 (s), 107.17 (t), 112.88 (t), 118.54 (t), 119.17 (t), 120.87 (q), 124.42 (t), 124.73 (q), 127.51 (t), 128.11 (t), 128.61 (t), 130.14 (t), 130.42 (t), 132.66 (q), 136.51 (t), 154.59 (q), 159.18 (q), 163.37 (q), 164.02 (q), 177.70 (q), 106.99 (q).

To a solution of 3′-(benzyloxy)-8-(ethoxycarbonyl)flavone (0.9 g, 2.25 mmol) in 25 mL of methanol was added 1.13 g (18 mmol) of ammonium formate and 0.01 g of palladium on charcoal (10% w/w). The mixture was refluxed until completion as indicated by TLC (ethyl acetate/petroleum ether, 1:10) (about 6 h). The hot reaction mixture was filtered, and the product was allowed to precipitate from the mother liquor. After filtration and washing with water, the crude product 8-(ethoxycarbonyl)-3′-hydroxyflavone was recrystallized from methanol, yield 51%, mp 224.5−225.5 °C. ^{1}H NMR (200 MHz, DMSO): δ 1.40 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.45 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 7.00−7.02 (m, 1H, H4′), 7.04 (s, 1H, H3), 7.34−7.42 (m, 1H, H6), 7.55−7.62 (m, 3H, H2′, H5′, H6′), 8.27−8.31 (m, 2H, H5, H7), 9.91 (br s, 1H, ArOH). ^{13}C NMR (50 MHz, DMSO): δ 13.88 (p), 61.38 (s), 106.52 (t), 113.02 (t), 117.17 (t), 118.83 (t), 120.51 (q), 123.99 (q), 124.75 (t), 129.45 (t), 129.93 (t), 131.96 (q), 136.05 (t), 153.47 (q), 157.66 (q), 162.59 (q), 163.53 (q), 176.20 (q).

A mixture of 8-(ethoxycarbonyl)-3′-hydroxyflavone (0.31 g, 1 mmol), 2-(chloromethyl)quinoline hydrochloride (0.24 g, 1.1 mmol), and potassium carbonate (0.28 g, 2 mmol) in 25 mL of DMF was stirred at 100 °C for 2 days (TLC monitoring: ethyl acetate/petroleum ether, 1:5). After cooling the reaction mixture was poured into 100 mL of water and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with water (100 mL) and brine (100 mL) and dried over sodium sulfate. Removal of the solvent yielded the crude product which was further purified by recrystallization from methanol, yield 13%, mp 161.4−162.5 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.42 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 5.43 (s, 2H, CH_2O), 6.82 (s, 1H, H3), 7.14−7.19 (m, 1H, H4′), 7.39−7.43 (m, 1H, H6), 7.54−7.59 (m, 1 H, H6-quinoline), 7.63 (d, 1H, ^3J = 8 .5 Hz, H3-quinoline), 7.73−7.77 (m, 1H, H7-quinoline), 7.82−7.85 (m, 1H, H5-quinoline), 8.01−8.09 (m, 4H, H8-quinoline, H5′, H6′, H2′), 8.21 (d, 1H, ^3J = 8.5 Hz, H4-quinoline), 8.30 (m, 1H, H5/7), 8.41 (m, 1H, H5/7). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.23 (p), 61.59 (s), 71.38 (s), 107.22 (t), 113.42 (t), 117.84 (t), 119.00 (t), 119.34 (t), 120.80 (q), 124.30 (t), 124.65 (q), 126.52 (t), 127.46 (q), 127.57 (t), 128.86 (t), 129.76 (t), 130.16 (t), 130.31 (t), 132.75 (q), 136.40 (t), 136.98 (t), 147.43 (q), 154.44 (q), 157.09 (q), 158.82 (q), 163.12 (q), 163.59 (q), 177.52 (q). Anal. ($C_{28}H_{21}NO_5$) C, H, N.

8-(Ethoxycarbonyl)-4′-[(2-quinolinyl)methoxy]flavone (10b). This compound was prepared in a similar way as described for **10a**, yield 64%, mp 165.1−166.3 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.44 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.47 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 5.46 (s, 2H, quinolineCH_2O), 6.77 (s, 1H, H3), 7.15 (d, 2H, ^3J = 9.0 Hz, H3′, H5′), 7.43 (t, 1H, ^3J = 7.7 Hz, H6), 7.51−7.59 (m, 1H, H6-quinoline), 7.64 (d, 1H, ^3J = 8.5 Hz, H3-quinoline), 7.71−7.77 (m, 1H, H7-quinoline), 7.78−7.84 (m, 1H, H5-quinoline), 8.02 (d, 2H, ^3J = 9.0 Hz, H2′, H6′), 8.07−8.11 (m, 1H, H8-quinoline), 8.20 (d, 1H, ^3J = 8.5 Hz, H4-quinoline), 8.27 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.8 Hz, H5 or H7), 8.40 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.8 Hz, H5 or H7). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.21 (p), 61.51 (s), 71.07 (s), 105.64 (t), 115.34 (t), 118.88 (t), 120.54 (q), 124.14 (t), 124.62 (q), 126.73 (t), 127.50 (q), 127.61 (t), 128.41 (t), 128.54 (t), 130.03 (t), 130.35 (t), 136.21 (t), 137.41 (t), 154.47 (q), 156.73 (q), 161.19 (q), 163.38 (q), 163.98 (q), 177.41 (q). Anal. ($C_{28}H_{21}NO_5$) C, H, N.

8-Carboxy-3′-[(2-quinolinyl)methoxy]flavone (11a). The flavone ester **10a** (50 mg, 0.11 mmol) was dissolved in a 250-mL mixture (1:1:1) of methanol, THF, and 5% LiOH water solution. The solution was stirred at room temperature for 24 h with TLC monitoring (ethyl acetate/petroleum ether, 1:5). The reaction mixture was then acidified with 3 M HCl, and the precipitate was collected by filtration and washed with water and ethanol. Recrystallization from DMF yielded the pure product, yield 40%, mp >300 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.48 (s, 2H, quinolineCH_2O), 7.23 (s, 1H, H3), 7.31 (dd, 1H, ^3J = 8.2 Hz, ^4J = 2.3 Hz, H4′), 7.51 (t, 1H, ^3J = 8.0 Hz, H5′), 7.58 (t, 1H, ^3J = 7.7 Hz, H6), 7.61−7.65 (m, 1H, H6-quinoline), 7.75 (d, 1H, ^3J = 8.5 Hz, H3-quinoline), 7.78−7.81 (m, 1H, H7-quinoline), 7.84−7.85 (m, 1H, H6′), 8.00−8.05 (m, 3H, H2′, H5-quinoline, H8-quinoline), 8.27 (dd, 1H, ^3J = 7.9 Hz, ^4J = 1.8 Hz, H5 or H7), 8.30 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.8 Hz, H5 or H7), 8.45 (d, 1H, ^3J = 8.5 Hz, H4-quinoline). ^{13}C NMR (50 MHz, DMSO): δ 70.84 (s), 106.65 (t), 112.37 (t), 118.51 (t), 119.11 (t), 119.70 (t), 121.46 (q), 123.97 (q), 124.73 (t), 126.48 (t), 127.01 (q), 127.78 (t), 128.33 (t), 129.10 (t), 129.74 (t), 130.16 (t), 132.21 (q), 136.17 (t), 136.91 (t), 146.72 (q), 153.62 (q), 156.90 (q), 158.47 (q), 161.94 (q), 165.08 (q), 176.48 (q).

8-Carboxy-4′-[(2-quinolinyl)methoxy]flavone (11b). This compound was prepared in a similar way as described for **11a**, yield 89%, mp 223.4−225.9 °C. ^{1}H NMR (400 MHz, DMSO, 350 K): δ 5.50 (s, 2H, CH_2O), 6.97 (s, 1H, H3), 7.27 (d, 2H, ^3J = 8.7 Hz, H3′, H5′), 7.52−7.56 (m, 1H, H6), 7.60−7.64 (m, 1H, H6-quinoline), 7.69 (d, 1H, ^3J = 8.4 Hz, H3-quinoline), 7.77−7.81 (m, 1 H, H7-quinoline), 7.98 (d, 1H, ^3J = 7.9 Hz, H5-quinoline), 8.03 (d, 1 H, ^3J = 8.4 Hz, H5-quinoline), 8.16 (d, 2H, ^3J = 8.7 Hz, H2′, H6′), 8.23−8.25 (m, 2H, H5, H7), 8.41 (d, 1H, ^3J = 8.4 Hz, H4-quinoline). ^{13}C NMR (100 MHz, DMSO): δ 71.00 (s), 104.92 (t), 115.21 (t), 119.21 (t), 121.70 (q), 123.42 (q), 123.86 (q), 124.23 (t), 126.20 (t), 126.89 (q), 127.48 (t), 128.10 (t), 128.24 (t), 128.54 (t), 129.40 (t), 135.29 (t), 136.62 (t), 146.73 (q), 153.37 (q), 156.56 (q), 160.98 (q), 162.28 (q), 164.73 (q), 175.86 (q). Anal. ($C_{26}H_{17}NO_5 \cdot 0.7H_2O$) C, H, N.

8-Carboxy-4′-[(2-naphthyl)methoxy]flavone (11c). This compound was prepared in a similar way as described for **11a**, yield 43%, mp 245.1−248.7 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.43 (s, 2H, CH_2O), 7.09 (s, 1H, H3), 7.28 (d, 2H, ^3J = 8.8 Hz, H3′, H5′), 7.57−7.65 (m, 4H, H6, 3H-naphthyl), 7.97−8.04 (m, 4H, 4H-naphthyl), 8.20−8.25 (m, 4H, H5, H7, H2′, H6′), 13.59 (br s, 1H, $ArCO_2H$). ^{13}C NMR (50 MHz, DMSO): δ 69.45 (s), 104.89 (t), 115.25 (t), 121.48 (q), 123.09 (q), 123.92 (q), 124.56 (t), 125.53 (t), 126.04 (t), 126.19 (t), 126.30 (t), 127.42 (t), 127.60 (t), 127.96 (t), 128.28 (t), 128.96 (t), 132.38 (q), 132.53 (q), 133.92 (q), 135.82 (t), 153.54 (q), 161.20 (q), 162.40 (q), 165.05 (q), 176.19 (q). Anal. ($C_{27}H_{18}O_5 \cdot 1.3H_2O$) C, H.

8-Carboxy-4′-[(2-quinazolinyl)methoxy]flavone (11d). This compound was prepared in a similar way as described for **11a**, yield 58%, mp 264.8−266.0 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.59 (s, 2H, CH_2O), 7.07 (s, 1H, H3), 7.25 (d, 2H, ^3J = 8.8 Hz, H3′, H5′), 7.56 (t, 1H, ^3J = 7.8 Hz, H6), 7.80−7.84 (m, 1H, H6-quinazoline), 8.17−8.19 (m, 2H, H5-quinazoline, H7-quinazoline), 8.21−8.28 (m, 5H, H5, H7, H2′, H6′, H8-quinazoline), 9.69 (s, 1H, H4-quinazoline), 13.51 (br s, 1H, $ArCO_2H$). ^{13}C NMR (50 MHz, DMSO): δ 70.58 (s), 104.89 (t), 115.14 (t), 121.51 (q), 123.15 (q), 123.30 (q), 123.91 (q), 124.54 (t), 127.31 (t), 127.68 (t), 128.01 (t), 128.24 (t), 128.93 (t), 134.77 (t), 135.79 (t), 149.10 (q), 153.52 (q), 161.14 (q), 161.21 (q), 161.30 (t), 162.38 (q), 165.03 (q), 176.19 (q). Anal. ($C_{25}H_{16}N_2O_5 \cdot H_2O$) C, H, N.

Method B. Ethyl 3-Acetyl-5-bromo-2-hydroxybenzoate (13). A solution of 5.18 g (20 mmol) of 3-acetyl-5-bromo-2-hydroxybenzoic acid in 100 mL of ethanol containing 5% sulfuric acid was refluxed for 5 h. The solvent was removed in vacuo. The crude product was dissolved in ethyl acetate, and the organic layer was washed with water, 10% $NaHCO_3$,

and brine. The organic layer was dried over sodium sulfate, and the solvent was removed. The benzoate **13** was obtained as a brown solid, yield 75%, mp 64.0−65.2 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.39 (t, 3H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 2.63 (s, 3H, $COCH_3$), 4.38 (q, 2H, ^3J = 7.2 Hz, $CO_2CH_2CH_3$), 8.00 (d, 1H, ^4J = 2.7 Hz, H4/6), 8.06 (d, 1H, ^4J = 2.7 Hz, H4/6), 12.07 (s, 1H, ArOH). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.96 (p), 30.67 (p), 62.14 (s), 110.56 (q), 116.59 (q), 127.18 (q), 137.38 (t), 138.57 (t), 160.42 (q), 167.66 (q), 198.09 (q).

Preparation of Methyl 3-Isopropoxybenzoate (12). A mixture of ethyl 3-hydroxybenzoate (6.64 g, 40 mmol), 2-bromopropane (9.84 g, 80 mmol), and potassium carbonate (11.04 g, 80 mmol) in 100 mL of DMF was stirred at 100 °C for 24 h. The reaction mixture was poured into water, and the product was extracted with ethyl acetate. The combined organic layers were washed with 1 N NaOH, water, and brine and dried over sodium sulfate. Removal of the solvent yielded **12** as a colorless oil, yield 49%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (d, 6H, ^3J = 6.0 Hz, $CH(CH_3)_2$), 3.88 (s, 3H, CO_2CH_3), 4.59 (h, 1H, ^3J = 6.0 Hz, $CH(CH_3)_2$), 7.05 (dd, 1H, ^3J = 8.2 Hz, ^4J = 2.6 Hz, H4), 7.30 (t, 1H, ^3J = 7.9 Hz, H5), 7.52 (m, 1H, H2), 7.57 (dd, 1H, ^3J = 7.6 Hz, ^4J = 1.6 Hz, H6).

6-Bromo-8-(ethoxycarbonyl)-3′-isopropoxyflavone (15). A solution of ethyl benzoate **12** (6.24 g, 30 mmol) and the acetophenone **13** (2.87 g, 10 mmol) in 50 mL of dioxane was slowly added to a suspension of 1.45 g (60 mmol) of NaH in 100 mL of dioxane. The reaction mixture was refluxed for 7 h. After cooling to room temperature the bulk of dioxane was removed in vacuo, and petroleum ether was added. The precipitate was collected by filtration and dissolved in water (200 mL). Acidification of the water solution afforded a brown precipitate (crude **14**) which was collected by filtration, dried in vacuo, and used in the next reaction without further purification.

The crude 1,3-propanedione **14** (4.0 g, 9 mmol) was dissolved in 50 mL of 99% formic acid and refluxed for 2 h. After cooling, the reaction mixture was diluted with ice water (100 mL). The precipitate was collected by filtration and dried in vacuo. The crude product was further purified by recrystallization from ethanol, yield 80%. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (d, 6H, ^3J = 6.0 Hz, $OCH(CH_3)_2$), 1.49 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.51 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.68 (heptet, 1H, ^3J = 6.0 Hz, $OCH(CH_3)_2$), 6.88 (s, 1H, H3), 7.06−7.10 (m, 1H, H4′), 7.43 (t, 1H, ^3J = 8.0 Hz, H5′), 7.58−7.65 (m, 2H, H2′, H6′), 8.39 (d, 1H, ^4J = 2.6 Hz, H5/7), 8.54 (d, 1H, ^4J = 2.6 Hz, H5/7). ^{13}C NMR (50 MHz, $CDCl_3$, DEPT): δ 14.15 (p), 21.84 (p), 61.97 (s), 70.10 (t), 106.96 (t), 113.63 (t), 118.54 (t), 119.54 (t), 130.06 (t), 132.71 (t), 138.88 (t).

6-Bromo-8-(ethoxycarbonyl)-3′-hydroxyflavone (16). A solution of 3′-isopropoxyflavone **15** (2.16 g, 5 mmol) in 25 mL of acetic acid containing 3% concentrated sulfuric acid was refluxed for 0.5 h. The reaction mixture was then poured into ice and extracted with ethyl acetate. The combined organic layers were washed with water and dilute $NaHCO_3$ and dried over Na_2SO_4. Evaporation of the solvent yielded the crude hydroxyflavone **16** as a brownish solid, which was further purified by recrystallization from ethanol, yield 80%, mp 242.3−243.6 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.47 (t, 3H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 4.48 (q, 2H, ^3J = 7.1 Hz, $CO_2CH_2CH_3$), 6.07 (br s, 1H, ArOH), 7.01 (s, 1H, H3), 7.04−7.06 (m, 1H, H4′), 7.39 (t, 1H, J = 8.0 Hz, H5′), 7.57−7.60 (m, 2H, H2′, H6′), 8.38 (d, 1H, J = 2.6 Hz, H5/7), 8.52 (d, 1H, J = 2.6 Hz, H5/7). ^{13}C NMR (50 MHz, DMSO): δ 13.81 (p), 61.83 (s), 106.57 (t), 113.08 (t), 116.78 (q), 117.25 (t), 119.04 (t), 122.82 (q), 125.68 (q), 129.97 (t), 131.29 (t), 131.69 (q), 137.89 (t), 151.90 (q), 157.68 (q), 162.12 (q), 162.86 (q), 175.02 (q).

Flavone-8-carboxylic Esters 17 and Acids 18. All esters **17** were prepared by alkylation of 3′-hydroxyflavone **16** with an appropriate arylmethyl chloride as described under **10a**, and the acids **18** were obtained by hydrolysis of the corresponding esters **17** as described under **11a**. Physicochemical data of individual compounds are listed below.

6-Bromo-8-carboxy-3′-[(2-quinolinyl)methoxy]flavone (18a): yield 75%, mp 241.6−242.0 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.47 (s, 2H, CH_2O), 7.27 (s, 1H, H3), 7.30−7.32 (m, 1H, H4′), 7.50 (t, 1H, ^3J = 8.0 Hz, H5′), 7.61−7.65 (m, 1H, H6-quinoline), 7.75 (d, 1H, ^3J = 8.5 Hz, H3-quinoline), 7.78−7.83 (m, 2H, H6′, H7-quinoline), 7.99−8.05 (m, 3H, H2′, H5-quinoline, H8-quinoline), 8.29 (br s, 1H, H5/7), 8.34 (br s, 1H, H5/7), 8.45 (d, 1H, ^3J = 8.3 Hz, H4-quinoline). ^{13}C NMR (50 MHz, DMSO): δ 70.81 (s), 106.69 (t), 112.37 (t), 116.81 (q), 118.69 (t), 119.18 (t), 119.67 (t), 123.82 (q), 125.65 (q), 126.49 (t), 127.02 (q), 127.79 (t), 128.31 (t), 129.76 (t), 130.17 (t), 130.93 (t), 131.91 (q), 136.94 (t), 138.05 (t), 146.70 (q), 152.61 (q), 156.87 (q), 158.45 (q), 162.19 (q), 163.77 (q), 175.26 (q). Anal. ($C_{26}H_{16}BrN_2O_5 \cdot 1.3H_2O$) C, H, N.

6-Bromo-8-carboxy-3′-[(2-naphthyl)methoxy]flavone (18b): yield 70%, mp 211.4−212.8 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.34 (s, 2H, CH_2O), 7.23 (s, 1H, H3), 7.24−7.28 (m, 1H, H4′), 7.45−7.70 (m, 4H, H-aromatic), 7.80−8.05 (m, 6H, H-aromatic), 8.29 (d, 1H, ^4J = 1.8 Hz, H5/7), 8.32 (d, 1H, ^4J = 1.8 Hz, H5/7).

6-Bromo-8-carboxy-3′-[(2-quinazolinyl)methoxy]flavone (18c): yield 41%, mp 245.7−245.9 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.54 (s, 2H, CH_2O), 7.16 (s, 1H, H3), 7.28 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.7 Hz, H4′), 7.48 (t, 1H, ^3J = 8.0 Hz, H5′), 7.76−7.79 (m, 2H, H6-quinazoline, H6′), 7.93 (s, 1H, H2′), 8.02−8.04 (m, 2H, H5-quinazoline, H7-quinazoline), 8.17 (d, 1H, ^3J = 8.0 Hz, H8-quinazoline), 8.29 (d, 1H, ^4J = 2.4 Hz, H5/7), 8.31 (d, 1H, ^4J = 2.4 Hz, H5/7), 9.65 (s, 1H, H4-quinazoline). Anal. ($C_{25}H_{15}BrN_2O_5 \cdot 1.2H_2O$) C, H, N, Br.

6-Bromo-8-carboxy-3′-[(2-benzothiazolyl)methoxy]flavone (18d): yield 52%, mp 250.7−251.4 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.70 (s, 2H, CH_2O), 7.22 (s, 1H, H3), 7.34−7.36 (m, 1H, H4′), 7.44−7.48 (m, 1H, H5), 7.52−7.56 (m, 2H, H5-benzothiazole, H6-benzothiazole), 7.84 (d, 1H, ^3J = 7.9 Hz, H6′), 7.98 (s, 1H, H2′), 8.00−8.04 (m, 1H, H4-benzothiazole), 8.10−8.12 (m, 1H, H7-benzothiazole), 8.31 (d, 1H, ^4J = 2.5 Hz, H5/7), 8.33 (d, 1H, ^4J = 2.5 Hz, H5/7).

6-Bromo-8-carboxy-3′-[(2-(1-methylbenzimidazolyl))-methoxy]flavone (18e): yield 82%, mp 287.4−288.5 °C. ^{1}H NMR (400 MHz, DMSO): δ 4.01 (s, 3H, NCH_3), 5.71 (s, 2H, CH_2O), 7.23 (s, 1H, H3), 7.41−7.50 (m, 3H, H4′, H5-benzimidazole, H6-benzimidazole), 7.56 (t, 1H, ^3J = 8.0 Hz, H5′), 7.77−7.81 (m, 2H, H4-benzimidazole, H7-benzimidazole), 7.87 (d, 1H, ^3J = 7.7 Hz, H6′), 8.00 (s, 1H, H2′), 8.31 (d, 1H, ^4J = 2.1 Hz, H5/7), 8.33 (d, 1H, ^4J = 2.1 Hz, H5/7). Anal. ($C_{25}H_{17}BrN_2O_5 \cdot HCl \cdot H_2O$) C, H, N.

6-Bromo-8-carboxy-3′-[(2-(7-chloroquinolinyl))methoxy]-flavone (18f): yield 68%, mp 269.0−269.1 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.47 (s, 2H, CH_2O), 7.27 (s, 1H, H3), 7.30 (dd, 1H, ^3J = 8.4 Hz, ^4J = 2.0 Hz, H4′), 7.51 (t, 1H, ^3J = 8.0 Hz, H5′), 7.55 (dd, 1H, ^3J = 8.7 Hz, ^4J = 1.7 Hz, H6-quinoline), 7.76 (d, 1H, ^3J = 8.5 Hz, H3-quinoline), 7.83 (d, 1H, ^3J = 7.7 Hz, H6′), 7.99 (s, 1H, H2′), 8.05−8.07 (m, 2H, H5-quinoline, H8-quinoline), 8.28 (d, 1H, ^4J = 2.4 Hz, H5/7), 8.33 (d, 1H, ^4J = 2.4 Hz, H5/7), 8.48 (d, 1H, ^3J = 8.5 Hz, H4-quinoline). ^{13}C NMR (50 MHz, DMSO): δ 70.62 (s), 106.64 (t), 112.34 (t), 116.78 (q), 118.68 (t), 119.23 (t), 120.02 (t), 125.60 (q), 125.63 (q), 126.98 (t), 127.10 (t), 129.77 (t), 130.16 (t), 130.68 (t), 131.94 (q), 134.24 (q), 136.98 (t), 137.97 (t), 147.03 (q), 152.53 (q), 158.28 (q), 158.36 (q), 162.14 (q), 163.82 (q), 17.27 (q).

6-Bromo-8-carboxy-4′-[(2-quinolinyl)methoxy]flavone (18g). To a solution of the 5′-bromo-3′-carboxy-2′-hydroxy-4-[(2-quinolinyl)methoxy]chalcone (0.52 g, 1 mmol) in 10 mL of glacial acetic acid was added dropwise 0.06 mL (1.1 mmol) of bromine. The reaction mixture was stirred at room temperature for 3 h. The yellow precipitate was filtered and washed with water. The dibromochalcone was dissolved in 8 mL of ethanol and 15 mL of 6% KOH solution; the reaction mixture was stirred for 4 more h. After acidification the precipitate was filtered and recrystallized from DMF, yield 38%, mp 261.2−263.9 °C. ^{1}H NMR (200 MHz, DMSO): δ 5.43 (s, 2H, quinolineCH_2O), 7.10 (s, 1H, H3), 7.26 (d, 2H, ^3J = 8.9 Hz, H3′, H5′), 7.60−7.66 (m, 1H, H6-quinoline), 7.69 (d, 1 H, ^3J = 8.5 Hz, H3-quinoline), 7.75−7.79 (m, 1H, H7-quinoline), 7.98−8.05 (m, 2H, H5-quinoline, H8-quinoline), 8.17 (d, 2H, ^3J = 8.9 Hz, H2′, H6′), 8.26 (d, 1H, ^4J = 1.8 Hz, H5 or H7),

8.28 (d, 1H, ^4J = 1.8 Hz, H5 or H7), 8.43 (d, 1H, ^3J = 8.5 Hz, H4-quinoline). ^{13}C NMR (50 MHz, DMSO): δ 70.83 (s), 104.94 (t), 115.24 (t), 116.60 (q), 116.63 (q), 119.43 (t), 123.03 (q), 125.58 (q), 126.49 (t), 126.99 (q), 127.76 (t), 128.33 (t), 128.39 (t), 129.74 (t), 130.58 (t), 136.94 (t), 137.59 (t), 146.72 (q), 152.23 (q), 156.70 (q), 161.12 (q), 162.59 (q), 163.75 (q), 174.97 (q). Anal. ($C_{26}H_{16}BrN_2O_5 \cdot 0.5H_2O$) C, H, N, Br.

6-Bromo-8-(benzenesulfonamido)-4′-[(2-quinolinyl)-methoxy]flavone (20). The flavone-8-carboxylic acid **18g** (0.50 g, 1.0 mmol) was dissolved in 10 mL of dry DMF together with 0.19 g (1.2 mmol) of benzenesulfonamide, 0.23 g (1.2 mmol) of EDCI, and 0.15 g (1.2 mmol) of DMAP. The reaction mixture was stirred under ultrasound conditions overnight and poured into water. The product was extracted with ethyl acetate; the combined organic layers were washed with 1 M HCl and brine and dried over sodium sulfate. Removal of the solvent and recrystallization from DMF/ethanol yielded the pure compound as a yellow solid, yield 16%, mp 255.6−256.5 °C. ^{1}H NMR (400 MHz, DMSO): δ 5.56 (s, 2H, CH_2O), 7.06 (s, 1H, H3), 7.18 (d, 2H, ^3J = 8.9 Hz, H3′, H5′), 7.62−7.69 (m, 4H, H3-phenyl, H4-phenyl, H5-phenyl, H6-quinoline), 7.72 (d, 1H, ^3J = 8.6 Hz, H3-quinoline), 7.79−7.83 (m, 1H, H7-quinoline), 7.87 (d, 2H, ^3J = 8.9 Hz, H2′, H6′), 8.02 (d, 1H, ^3J = 8.1 Hz, H5-quinoline), 8.05−8.07 (m, 3H, H8-quinoline, H2-phenyl, H6-phenyl), 8.13 (d, ^4J = 2.4 Hz, H5/7), 8.21 (d, 1H, ^4J = 2.4 Hz, H5/7), 8.46 (d, 1H, ^3J = 8.6 Hz, H4-quinoline). ^{13}C NMR (50 MHz, DMSO): δ 71.07 (s), 105.46 (t), 115.48 (t), 117.08 (q), 119.67 (t), 122.99 (q), 125.20 (q), 126.79 (t), 127.27 (q), 127.65 (t), 127.79 (t), 128.06 (t), 128.43 (t), 128.56 (t), 129.19 (t), 130.07 (t), 133.84 (t), 136.16 (t), 137.28 (t), 139.28 (q), 142.85 (q), 146.98 (q), 151.45 (q), 157.05 (q), 161.31 (q), 162.24 (q), 162.57 (q), 175.00 (q). HRMS: *m/e* [M$^+$] calcd, 640.0304; found, 640.0317 ± 0.0003. Anal. ($C_{32}H_{21}BrN_2O_6S \cdot 1.0H_2O$) C, H, N, S; Br: calcd, 12.12; found, 12.70.

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Supporting Information Available: Table of NOE difference spectroscopy for **5b**,**c** and **11a** (1 page). Ordering information is given on any current masthead page.

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