Synthesis and Biological Evaluation of 2-Phenylpyran-4-ones: A New Class of Orally Active Cyclooxygenase-2 Inhibitors

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A series of 2-phenylpyran-4-ones were prepared and evaluated for their ability to inhibit cyclooxygenase-2 (COX-2). Extensive structure−activity relationship work was carried out within this series, and a number of potent and selective COX-2 inhibitors were identified. Compounds having a *p*-methylsulfone group at the 2-phenyl ring showed the best COX-2 inhibitory activity. The introduction of a substituted phenoxy ring at position 3 enhanced both the in vitro and in vivo activity within the series. A selected group of 3-phenoxypyran-4-ones exhibited excellent activity in an experimental model of pyresis. The in vivo antiinflammatory activity of these compounds was confirmed with the evaluation of their antiarthritic and analgesic effectiveness. Moreover, their pharmacokinetic profile in rats is compatible with a once a day administration by oral route in humans. Within this novel series, compounds **21**, **31**, **34**, and **35** have been selected for further preclinical and clinical evaluation.

Introduction

The discovery and characterization of the cyclooxygenase-2 (COX-2) enzyme early in the 1990s[1] led to the hypothesis that selective inhibitors of this isoform would exhibit similar clinical efficacy but reduced ulcerogenicity than traditional nonsteroidal antiinflammatory drugs (NSAIDs), which were nonselective COX-1 and COX-2 inhibitors. Less than a decade after the COX-2 finding, celecoxib[2] (Celebrex, Pfizer) and rofecoxib[3] (Vioxx, Merck) (Figure 1) were launched, inaugurating a new class of antiinflammatory agents, the coxibs. The extensive clinical data published to date support both the efficacy of these drugs in the management of pain and inflammation[4,5] and their improved ulcerogenic profile.[6]

The potential therapeutic applications of coxibs have been expanded beyond the areas of analgesia and inflammation. In recent years, studies on COX-2 have been mainly focused on cancer and neurodegenerative disorders. The first results came from studies using mouse models of colon cancer[7] and suggested that COX-2 could be a useful target for the prevention and treatment of this devastating disease. In 1999, celecoxib was approved as an adjunctive therapy for familial adenomatous polyposis (FAP), an inherited form of colorectal cancer. In vitro studies with human cell cancer lines and in vivo experiments with rodents suggest that COX-2 inhibitors may also be useful for the treatment of other epithelial cancers from breast, prostate, bladder, lung, and pancreas.[8−10] In the field of neurodegenerative disorders, preliminary studies suggest a role for COX-2 in Parkinson's disease[11] whereas results on Alzheimer's disease did not fulfill the initial expectations.[12] The concern about the potential increased risk of cardiovascular events associated with coxibs still remains to be clarified and will determine the future applications of these compounds.

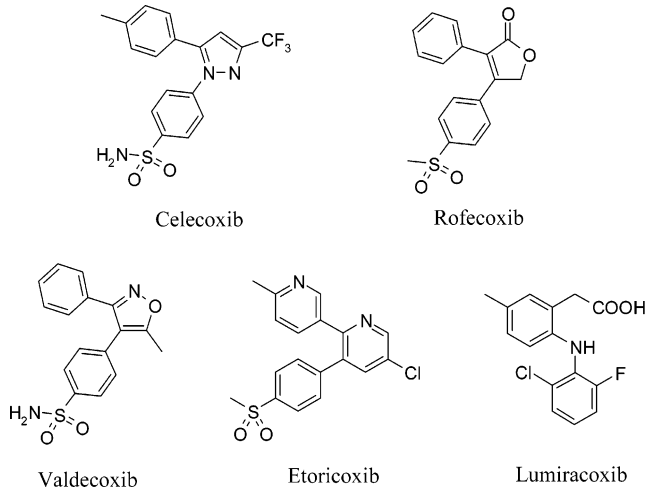

Figure 1. Structures of some selective COX-2 inhibitors.

In the past 5 years, three new compounds were evaluated in clinical trials: valdecoxib[13] (Bextra, Pfizer), etoricoxib[14](Arcoxia, Merck), and lumiracoxib[15] (Prexige, Novartis) (Figure 1). The second-generation COX-2 inhibitors were more selective for COX-2 over COX-1 compared to celecoxib and rofecoxib. Nevertheless, they display an overall pharmacological profile similar to the profile of first-generation coxibs. In this paper, we report the characterization of a new coxib series, the 2-phenylpyran-4-ones, a family of orally active, potent, and very selective COX-2 inhibitors with one of the best antiinflammatory profiles reported in animal models.

Chemistry

The general synthetic strategy employed to prepare the 2-phenylpyran-4-one derivatives was based on a cyclodehydration reaction of phenacyl derivatives using PPA in AcOH. As shown in Scheme 1, a series of 2-(4-

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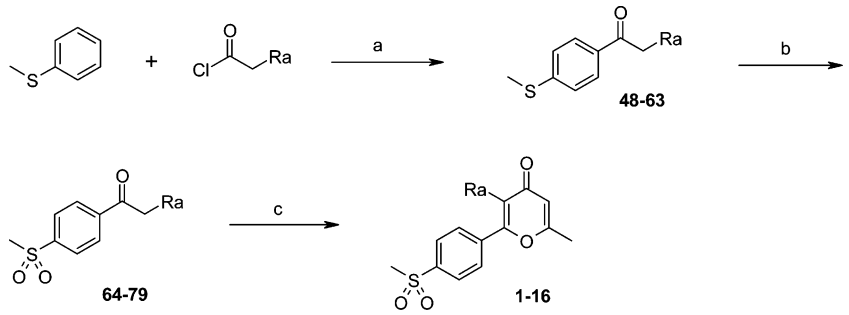
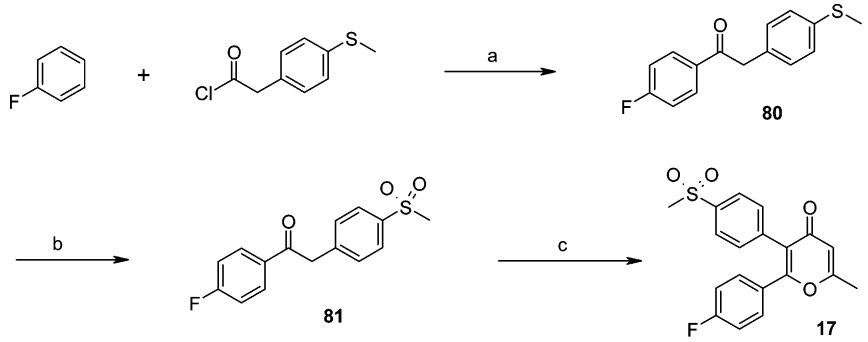
Scheme 1[a]



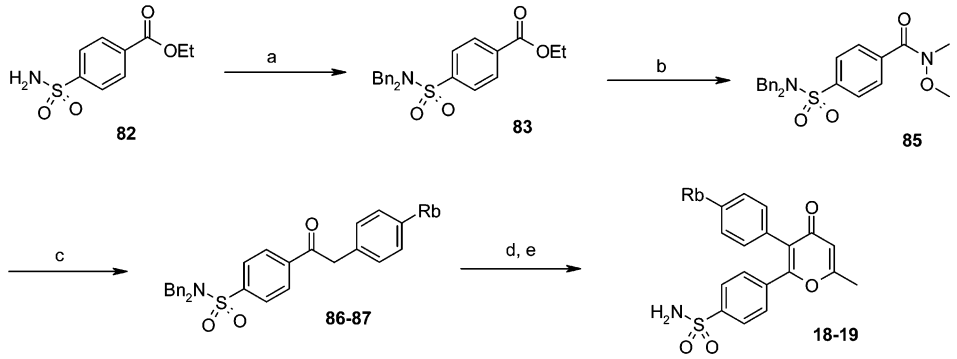
[a] Reagents: (a) $AlCl_3$, CH_2Cl_2; (b) MMPP, CH_2Cl_2/MeOH; (c) PPA, AcOH, 140 °C.

Scheme 2[a]



[a] Reagents: (a) $AlCl_3$, CS_2; (b) MMPP, CH_2Cl_2/MeOH; (c) PPA, AcOH, 140 °C.

Scheme 3[a]



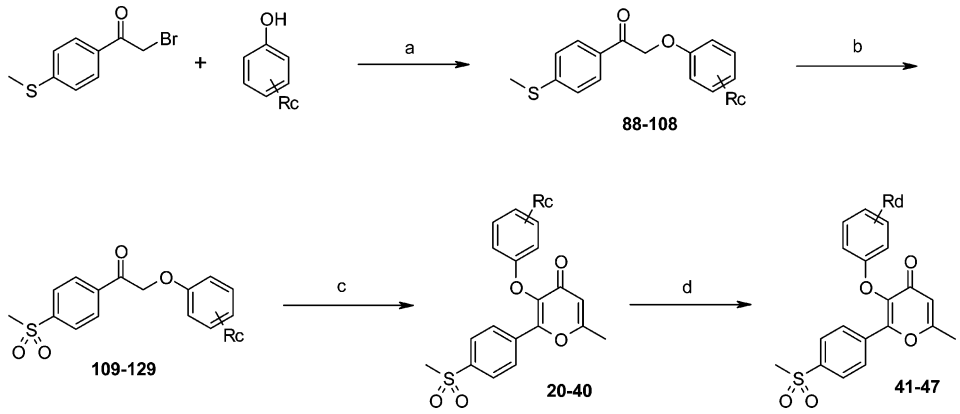
[a] Reagents: (a) BnCl, K_2CO_3, acetone; (b) (i) NaOH, EtOH; (ii) $SOCl_2$, CH_3NHOCH_3, Et_3N; (c) $RbPhCH_2MgCl$, THF; (d) PPA, AcOH, 140 °C; (e) H_2SO_4(conc).

methanesulfonylphenyl)pyran-4-one derivatives **1**−**16** were prepared from the corresponding phenacyl derivatives **64**−**79** by heating in a mixture of PPA in AcOH at 140 °C. The phenacyl derivatives **64**−**79** were prepared from (methylthio)benzene via Friedel−Craft reaction with the corresponding acyl chlorides, followed by oxidation of the thioethers to the sulfones using magnesium monoperoxiphthalate. The synthesis of the isomer 3-(4-methanesulfonylphenyl)pyran-4-one **17** (Scheme 2) was achieved by the same cyclodehydration reaction procedure using PPA in AcOH, starting from the phenacyl compound **81**. Compound **81** was available through a Friedel−Crafts reaction and oxidation sequence starting from fluorobenzene and [4-(methylthio)-phenyl]acetyl chloride.

The sulfonamide derivatives **18** and **19** were obtained from the corresponding phenacylsulfonamide intermediates **86** and **87** via the same cyclodehydration procedure described above (see Scheme 3). Compounds **86** and **87** were obtained from the commercially available ethyl 4-(aminosulfonyl)benzoate in five steps, comprising the protection of the sulfonamide to the dibenzylsulfonamide **83**, formation of the Weinreb amide **85**, Grignard reaction with the corresponding benzylmagnesium halides, followed by cyclization with PPA/AcOH, and finally, deprotection to the primary sulfonamide.

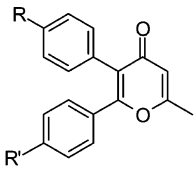
Scheme 4 outlines the preparation of 2-(4-methanesulfonylphenyl)-3-phenoxypyran-4-ones **20**−**47**. Alkylation of the diversely substituted phenols with 2-bromo-1-(4-methanesulfonylphenyl)ethanone[16] in the presence of potassium carbonate and tetrabutylammonium hydrogen sulfate in a mixture of dichloromethane/water yielded the intermediates **88**−**108**. These intermediates were oxidized with magnesium monoperoxiphthalate to the corresponding sulfones **109**−**129**. These sulfones were subjected to cyclodehydration to yield compounds **20**−**40**. It is worthy to note that the substitution on the phenol ring is very important in the final cyclization step. Electron-withdrawing groups are well tolerated, but electron-donating groups produce a significant

Scheme 4[a]



[a] Reagents: (a) K_2CO_3, tetrabutylammonium hydrogen sulfate, CH_2Cl_2/H_2O; (b) MMPP, CH_2Cl_2/MeOH; (c) PPA, AcOH, 120 °C; or PPA, Ac_2O, 100 °C; (d) functional group transformations (see Experimental Section).

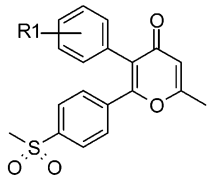
Table 1. 2,3-Diarylpyran-4-ones as Cyclooxygenase Inhibitors: *p*-Methylsulfone versus *p*-Sulfonamide Derivatives



Compd.	R	R'	COX-1[a]	COX-2[a]	COX-1/COX-2
1	H	SO_2Me	>100	1.84 ± 0.43	> 54
4	F	SO_2Me	>100	1.07 ± 0.01	> 93
17	SO_2Me	F	n.t.	9.77 ± 2.12	--
18	H	SO_2NH_2	n.t.	6.89 ± 3.49	--
19	F	SO_2NH_2	n.t.	>10	--
Rofecoxib			11.4 ± 0.6	0.76 ± 0.26	15
Etoricoxib			98.8 ± 6.2	0.81 ± 0.05	122

[a] Data are indicated as IC_{50} (μM). n.t.: not tested.

Table 2. 3-Phenylpyran-4-ones as Cyclooxygenase Inhibitors



Compd.	R1	COX-1[a]	COX-2[a]	COX-1/COX-2	Pyresis[b]
1	H	>100	1.84 ± 0.43	> 54	0 (10)
2	2-F	>100	1.53 ± 0.13	> 65	21 (10)
3	3-F	>100	3.37 ± 1.34	> 30	n.t.
4	4-F	>100	1.07 ± 0.01	> 93	21 (10)
5	4-Cl	>100	2.15 ± 0.04	> 46	3.5
6	4-Br	>100	1.73 ± 0.04	> 57	7.9
7	4-CF_3	n.t.	6.92 ± 0.72	--	n.t.
8	4-CH_3	>100	2.18 ± 0.55	> 46	n.t.
9	3,4-diCl	37.1 ± 15.5	0.68 ± 0.20	54	2.7
10	2,4-diF	>100	1.12 ± 0.04	> 89	29 (10)
11	2-F,4-Cl	>100	2.05 ± 0.35	> 48	53 (10)
Rofecoxib		11.4 ± 0.6	0.76 ± 0.26	15	0.9
Etoricoxib		98.8 ± 6.2	0.81 ± 0.05	122	1.0

[a] Data are indicated as IC_{50} (μM). [b] Data are indicated as ED_{50} (mg/kg) using four doses (six to eight animals per group) or percentage of inhibition (in parentheses) at 10 mg/kg (six to seven animals). Since SEM values never exceeded 15% of the media, they have been omitted. n.t.: not tested.

decrease in the final step yield. With that in mind, compounds **41**−**47**, which contain substituents such as amino or methyl groups, were prepared by conventional functional group transformations.

Biology

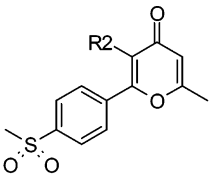
All compounds described herein were tested for their ability to inhibit human COX-1 and COX-2 using the whole blood assay described by Patrignani et al.[17] Potent and selective COX-2 inhibitors were evaluated in vivo in the yeast-induced pyresis model in rat. Compounds showing good oral activity in this model were then tested in an assay of inflammatory pain (Atkinson hyperalgesia model) and in a chronic model of inflammation (adjuvant-induced arthritis). The pharmacokinetic profile of a selected group of compounds was also evaluated in the rat.

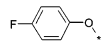
Results and Discussion

Structure−Activity Relationship. In the diaryl heterocyclic class of COX-2 inhibitors, it has been well established that a *p*-methylsulfone or sulfonamide on one of the phenyl groups is a requirement for good COX-2 potency and selectivity.[2,3,13,14,16] In the 2,3-diarylpyran-4-one series, we found that only compounds with the *p*-methylsulfone substitution on the 2-phenyl ring were active (see Table 1, compounds **1** and **4** vs **17**). Surprisingly, sulfonamide derivatives did not show good inhibitory activity in the HWB COX-2 assay (compounds **18** and **19**).[18] So taking into account this structural restriction, we initiated the structure−activity relationship work using 2-(4-methanesulfonylphenyl)pyran-4-one as a template, maintaining a methyl group at position 6 while exploring different modifications at position 3.

Our starting point was the 2-phenylpyran-4-one series. Most of the explored substituents showed comparable activities in the COX-2 assay and excellent COX-1/COX-2 selectivity (Table 2). The 2- and 4-fluoro derivatives (compounds **2** and **4**, respectively) were slightly more potent than compound **3** (3-fluoro) and were both inactive in the pyresis assay. Other halogen substitutions, such as 4-chloro (compound **5**) or 4-bromo (compound **6**), slightly decrease the COX-2 activity compared to that of compound **4** but dramatically increased the in vivo activity. Combinations of halogen atoms at the 3-phenyl ring also produced active compounds. The most interesting one was compound **9** (3,4-

Table 3. 3-Substituted Pyran-4-ones as Cyclooxygenase Inhibitors



Compd.	R2	COX-1[a]	COX-2[a]	COX-1/COX-2	Pyresis[b]
12		>100	2.59 ± 1.01	> 38	n.t.
13		n.t.	>10	--	n.t.
14		n.t.	6.55 ± 1.85	--	n.t.
15		>100	1.47 ± 0.14	> 68	7 (10)
16		n.t.	6.40 ± 0.90	--	n.t.
20		>100	0.98 ± 0.27	> 102	1.9
Rofecoxib		11.4 ± 0.6	0.76 ± 0.26	15	0.9
Etoricoxib		98.8 ± 6.2	0.81 ± 0.05	122	1.0

[a] Data are indicated as IC_{50} (μM). [b] Data are indicated as ED_{50} (mg/kg) using four doses (six to eight animals per group) or percentage of inhibition (in parentheses) at 10 mg/kg (six to seven animals). Since SEM values never exceeded 15% of the media, they have been omitted. n.t.: not tested.

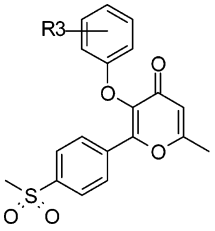
dichloro), with a COX-2 activity comparable to the activity of the reference compounds rofecoxib and etoricoxib and with a 54-fold COX-2 selectivity. Furthermore, it was the most active compound in the pyresis model.

In summary, the substituted 3-phenylpyran-4-one series has been identified as a promising new class of COX-2 inhibitors. However, these compounds were less active, both in vitro and in vivo, than the reference compounds rofecoxib and etoricoxib. To improve their activity, synthetic efforts were focused on the exploration of new substituents preferably at position 3 (Table 3). In this sense, several substituents were introduced at this position, such as other aromatic rings (compounds **12** and **13**), an alkyl group (compound **14**), a cycloalkyl group (compound **15**), and a benzyl group (compound **16**). Only compound **15** showed a COX-2 activity and selectivity similar to those of the previous analogues but with a lack of in vivo activity in the pyresis assay. Last, we found that the introduction of a 4-fluorophenoxy substituent at position 3 (compound **20**) was a good choice to achieve the best balance between both in vitro and in vivo activities. Thus, compound **20** became the lead compound of a new series, the 3-phenoxypyran-4-ones.

Within the 3-phenoxypyran-4-one derivatives (Table 4), the presence of halogen atoms in the para position of the 3-phenoxy ring generally enhanced the COX-2 activity with respect to the unsubstituted analogue **41** (compounds **21**, **24**, and **25**). All these halogenated compounds showed very good COX-1/COX-2 selectivity, especially the *p*-chloro derivative **21**, which is the most selective compound of this series. The 2- and 4-methyl derivatives (compounds **42** and **44**, respectively) were around 7-fold more potent than compound **43** (3-methyl substituted). Compound **46** with a *p*-amino group was less potent than the previous analogues (i.e., compounds **20**, **21**, **24**, **25**, and **44**) but was quite selective for COX-2. Compounds **26** and **28**, with 4-trifluoromethyl and 4-trifluoromethoxy groups, respectively, showed a decrease in COX-2 potency but still retained good selectivity. Other para monosubstituted derivatives with electron-withdrawing groups (**27**, **29**, **30**, and **47**) were inactive as COX-2 inhibitors. The oral testing of a subset of monosubstituted phenoxy derivatives revealed that only compounds **20** and **21** were active in the pyresis assay. With regard to the disubstituted derivatives, several combinations of halogen atoms, methyl groups, and methoxy groups were also tested. Some of them were very potent at inhibiting the COX-2 assay and also very selective (compounds **31**, **34**−**40**, and **45**). Indeed, compounds **31** and **45** were the most active compounds of this series, having a COX-2 activity in the nanomolar range. Moreover, the in vivo activity in the pyresis assay was clearly improved for compounds **31** and **34**.

In conclusion, within the 2-phenylpyran-4-one series, we have identified potent and selective COX-2 inhibitors with promising preliminary in vivo activity.

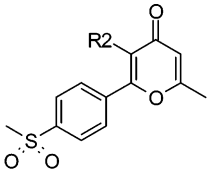
Table 4. 3-Phenoxypyran-4-ones as Cyclooxygenase Inhibitors



Compd.	R3	COX-1[a]	COX-2[a]	COX-1/COX-2	Pyresis[b]
20	4-F	>100	0.98 ± 0.27	>102	1.9
21	4-Cl	207 ± 114	0.32 ± 0.12	647	2.2
24	4-Br	119 ± 15	0.36 ± 0.18	330	46 (10)
25	4-I	>100	0.41 ± 0.23	>244	32 (10)
26	4-CF_3	>100	2.45 ± 1.03	>40	10 (10)
27	4-CF_3CF_2	n.t.	>10	--	n.t.
28	4-CF_3O	>100	1.44 ± 0.57	>69	31 (10)
29	4-NO_2	>100	3.99 ± 0.16	>25	n.t.
30	4-$COOCH_3$	n.t.	>10	--	n.t.
31	2,4-diF	22.3 ± 8.2	0.08 ± 0.05	279	0.7
32	3,4-diF	n.t.	4.43 ± 0.04	--	n.t.
33	3,4-diCl	>100	3.38 ± 1.33	>29	n.t.
34	2-F,4-Cl	18.8 ± 3.6	0.20 ± 0.06	94	0.8
35	2-F,4-Br	22.8 ± 5.5	0.15 ± 0.04	152	3.2
36	2-Cl,4-Br	35.2 ± 1.8	0.31 ± 0.10	113	37 (10)
37	4-F,2-CH_3	21.2 ± 1.40	0.18 ± 0.03	118	57 (10)
38	2-Cl,4-CH_3	16.6 ± 0.3	0.24 ± 0.01	69	18 (10)
39	4-Cl,2-CH_3	36.6 ± 1.9	0.19 ± 0.06	192	33 (10)
40	2-Cl,4-CH_3O	13.7 ± 3.8	0.18 ± 0.02	76	20 (10)
41	H	>100	1.00 ± 0.38	>100	22 (10)
42	2-CH_3	22.8 ± 2.9	0.17 ± 0.08	134	16 (10)
43	3-CH_3	>100	1.35 ± 0.21	74	17 (10)
44	4-CH_3	39.0 ± 18.8	0.21 ± 0.01	186	10 (10)
45	2-F,4-CH_3	6.90 ± 0.60	0.06 ± 0.04	115	12 (10)
46	4-NH_2	>100	1.48 ± 0.76	>67	8 (10)
47	4-COOH	n.t.	>10	--	n.t.
Rofecoxib		11.4 ± 0.6	0.76 ± 0.26	15	0.9
Etoricoxib		98.8 ± 6.2	0.81 ± 0.05	122	1.0

[a] Data are indicated as IC_{50} (μM). [b] Data are indicated as ED_{50} (mg/kg) using four doses (six to eight animals per group) or percentage of inhibition (in parentheses) at 10 mg/kg (six to seven animals). Since SEM values never exceeded 15% of the media, they have been omitted. n.t.: not tested.

Table 5. In Vivo Pharmacological Profile of Selected Pyran-4-ones



Compound	R2	Adjuvant arthritis[a]	Hyperalgesia[b]
5	4-Cl-C_6H_4-	1.000	50 ± 8
6	4-Br-C_6H_4-	0.700	42 ± 8
9	3,4-diCl-C_6H_3-	0.250	42 ± 8
20	4-F-C_6H_4-O-	0.220	42 ± 7
21	4-Cl-C_6H_4-O-	0.300	51± 5
31	2,4-diF-C_6H_3-O-	0.015	69 ± 6
34	2-F,4-Cl-C_6H_3-O-	0.050	54 ± 6
35	2-F,4-Br-C_6H_3-O-	0.008	61 ± 6
Rofecoxib		0.300	60 ± 9
Etoricoxib		0.440	35 ± 6

[a] Data are indicated as ED_{50} (mg/kg) using four doses (six to eight animals per group). [b] Data are indicated as percentage of inhibition at 3 mg/kg ± SEM (six to seven animals).

Table 6. Pharmacokinetic Profile of Selected 3-Phenoxypyran-4-ones after Oral Administratrion of 10 mg/kg

Compound	C_{max}[a]	AUC $_{0\text{-}24h}$[b]	$t_{1/2}$[c]	Plasma Protein Binding
21	5.4 ± 1.2	69.0 ± 17.3	2.6 ± 0.5	98.2
31	6.8 ± 0.5	90.2 ± 16.6	4.5 ± 0.8	98.4
34	2.0 ± 0.5	23.4 ± 4.5	3.3 ± 0.5	97.5
35	0.9 ± 0.1	10.9 ± 1.4	3.6 ± 0.4	93.9

[a] Data (μg/mL) are obtained using three animals per group. [b] Data (μg·h/mL) are obtained using three animals per group. [c] Data (h) are obtained using three animals per group.

In Vivo Activity. Selected compounds were evaluated in the adjuvant-induced arthritis model and the Atkinson hyperalgesia assay (Table 5). In the 3-phenylpyran-4-one series, only compound **9** showed good activity in vivo, with a potency in both assays similar to the potency of rofecoxib and etoricoxib. Unfortunately, this compound was hepatotoxic in rat (data not shown), and further characterization of this series was discontinued.

In the 3-phenoxypyran-4-one series, compounds not only displayed a high potency and selectivity for COX-2 in vitro but also showed good oral activity in vivo. In the Atkinson assay, this series showed an efficacy comparable to the efficacy of reference compounds. However, in the model of chronic inflammation, compounds **31**, **34**, and **35** exhibited excellent activity, with potencies from 35- to 50-fold higher than the potencies of rofecoxib and etoricoxib.

Some of the 3-phenoxypyran-4-ones (**21**, **31**, **34**, and **35**) were selected for pharmacokinetic studies. Although compounds **21** and **31** showed a better pharmacokinetic profile than compounds **34** and **35**, the four compounds exhibited a similar in vivo activity possibly because of differences in protein binding (Table 6).

The evaluation of compounds **21**, **31**, **34** and **35** on gastrointestinal toxicity showed that they did not cause any ulceration or hemoglobin loss after a 4-day treatment at 100 mg kg^{-1} day^{-1} (data not shown).[16]

In conclusion, selected 3-phenoxypyran-4-ones display a favorable pharmacological profile relative to the reference compounds rofecoxib and etoricoxib. Their excellent in vivo activity and lack of gastrointestinal side effects support the clinical development of these compounds in inflammation and pain. The evaluation of the 3-phenoxypyran-4-ones in animal models of cancer and neurodegenerative disorders is in progress.

Conclusions

We have identified the 2-phenylpyran-4-ones as a novel series of highly potent and selective COX-2 inhibitors and demonstrated that the *p*-methylsulfone group at the 2-phenyl ring gives the best COX-2 inhibitory activity. Of all the substituents introduced on the pyranone, the 3-aryloxy provided the most interesting compounds in terms of in vitro and in vivo activity. A further enhancement in activity was observed with halogen-substituted 3-aryloxypyranones, with activities in the nanomolar range. A selected group of 3-phenoxypyran-4-ones exhibited excellent oral activity when tested in assays of chronic inflammation, fever, and pain. Moreover, the good pharmacokinetic profile in rats of a selected group of 3-phenoxypyran-4-ones may be compatible with a once a day oral administration in humans. Furthermore, these compounds were devoid of gastrointestinal toxicity at high doses. Within this pyranone class, the 3-phenoxypyran-4-ones represent an improvement not only in the COX-2 potency and selectivity but also in the oral biological activity. To our knowledge, some of these compounds display some of the best antiarthritic activities reported in animal models. On the basis of their in vivo profile and lack of gastrointestinal toxicity, compounds **21**, **31**, **34**, and **35** have been selected for further preclinical and clinical evaluation. Results of these studies will be reported in due course.

Experimental Section

1. Biology. General. COX-2 and COX-1 activity in human whole blood, Atkinson hyperalgesia model in rat, adjuvant-induced arthritis model in rat, and the yeast-induced pyresis model in rat were performed as described previously.[16] For all the in vivo assays, male Wistar rats (Interfauna Iberica, Spain) were used. Unless otherwise indicated, rats were fasted with free access to water for 18 h prior to the assay. Statistic analysis between the different treatment groups was calculated according to the analysis of variance (ANOVA) test. A value of $p < 0.05$ was considered to be significant. The appropriate animal ethics committees have approved all the experimental protocols used in this paper.

2. Pharmacokinetics in Rats. Compounds were administered by oral route to fasted male Wistar rats. At different time points, blood samples were obtained and the blood and plasma content was analyzed by HPLC as described below. Pharmacokinetic parameters were determined by noncompartmental analysis using WinNonlin (Pharsight, Inc., Mountain View, CA).

3. HPLC Analysis for Pharmacokinetic Studies. Plasma levels (for compounds **21**, **31**, **34**, and **35**) were determined by an isocratic HPLC (515 pump, Waters) and UV detection (λ = 270−280 nm, UV2487 Waters) method using an on-line solid-phase system (PROSPEKT, Spark-Holland) assisted by a sampling injector (ASPEC XL, Gilson). Briefly, 1 mL of 20 mM, pH 4, sodium acetate buffer was added to 5 mL of disposable conical tubes containing 100 μL of plasma (200 μL for compound **21**). The mixture was shaken for 15 s with a vortex and centrifuged at 4000 rpm for 10 min (Megafuge 1.0R, Heraeus). Samples were then loaded into a Gilson sample processor. The on-line solid-phase extraction was carried out by the PROSPEKT system connected to a Gilson sample injector, using C2 and Oasis (for compounds **34** and **35**) cartridges (Baker and WATERS, respectively). The passage of the fluids through the cartridges was carried out by the

ASPEC sampling injector, using the following sample preparation steps: (1) activate the cartridge with 1.5 mL of methanol (acetonitrile for compounds **34** and **35**); (2) condition the cartridge with 1.5 mL of water; (3) load the sample; (4) wash the sample with 3 mL of water (for compound **31**), with 1 mL of methanol/water (10:90, v/v) and 2 mL of water (for compound **21**), with 2 mL of water and 1 mL of methanol/water (20:80, v/v, for compound **34**), or with 2 mL of water and 1 mL of methanol/water (60:40, v/v for compound **35**). Finally the elution from the analytical column (RP8 (for compound **21**) or C18, 150 mm × 4.6 mm, 5 μm, Symmetry, WATERS) was carried out by passage through the cartridge mobile phase for 0.5 min at a flow rate of 1 mL/min. The mobile phase was a mixture of acetonitrile and 20 mM sodium phosphate containing 0.2% of triethylamine (pH 7 for compound **21** and pH 3 for compound **31**) or 10 mM sodium phosphate buffer, pH 3 (for compounds **34** and **35**). The corresponding isocratic methods were 40% of organic for compound **21**, 35% of organic for compound **31**, 39% of organic for compound **34**, and 41% of organic for compound **35**. With these conditions, all compounds had a retention time in between 9 and 12 min.

4. Determination of Plasma Protein Binding (PPB). Aliquots of 1 mL of pooled human plasma were incubated with 2.5 μg/mL of test compound at 37 °C for 2 h. Samples were then transferred to a Centrifree micropartition device (Millipore, Bedford, MA) and centrifuged at 2000*g* for 15 min. Calibration standards of 25 and 250 ng/mL of each compound in PBS were used to quantify the samples. An amount of 100 μL of the ultrafiltrate or of calibration standard was diluted (1:1) with acetonitrile/water (50:50, v/v) and injected into the HPLC/MS system. Protein-free compound levels were determined by an isocratic HPLC (Alliance 2790 Waters) and MS detection (ZMD, Micromass, mode SIR) method.

5. Chemistry. General. Reagents, starting materials, and solvents were purchased from commercial suppliers and used as received. All organic solutions were dried over sodium sulfate. Concentration refers to evaporation under vacuum using a Büchi rotatory evaporator. Reaction products were purified, when necessary, by flash chromatography on silica gel (40−63 μm) with the solvent system indicated. Spectroscopic data were recorded on a Varian Gemini 300 spectrometer. Melting points were recorded on a Büchi 535 apparatus. Where analyses are indicated only by symbols of the elements, results obtained were within 0.4% of the theoretical values. The chromatographic separations were obtained using a Waters 2795 system equipped with a Symmetry C18 (2.1 mm × 100 mm, 3.5 μm) column. The mobile phase was formic acid (0.46 mL), ammonia (0.115 mL), and water (1000 mL) (solution A) and formic acid (0.4 mL), ammonia (0.1 mL), methanol (500 mL), and acetonitrile (500 mL) (solution B): initially from 0% to 95% of solution B in 20 min and then 4 min with 95% of solution B. The reequilibration time between two injections was 5 min. The flow rate was 0.4 mL/min. The injection volume was 5 μL. Also, a Kromasil C18 (4.61 × 100 mm, 5 μm) column was used. The mobile phase was 0.01 M phosphoric acid, 1 N sodium hydroxyde at pH 3 (A) and acetonitrile (B): initially from 0% to 83% of B in 55 min and then 15 min with 83% of B. The reequilibration time between two injections was 5 min. The flow rate was 1 mL/min. The injection volume was 10 μL. Diode array chromatograms were processed at 210 nm.

5.1. Synthesis of Pyrones 1−16 (Scheme 1). General Procedure for the Synthesis of Intermediates 48−63. Method A. 1-(4-Methylsulfanylphenyl)-2-phenylethanone (48). To a cooled solution of 7.30 g (58.8 mmol) of thioanisole and 10.2 g (76.5 mmol) of aluminum trichloride in 90 mL of dry CH_2Cl_2 was added dropwise a solution of 10.0 g (64.7 mmol) of phenylacetyl chloride in 20 mL of dry CH_2Cl_2. The mixture was stirred at room temperature for 2.5 h and poured into 6 N HCl/ice. The aqueous layer was separated and extracted with CH_2Cl_2. The combined organic phase was washed with saturated $NaHCO_3$, dried, and evaporated. The resulting solid was crystallized from ethyl ether to give 14.4 g (92%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.24 (s, 2H), 7.20−7.35 (m, 7H), 7.92 (d, J = 8.5 Hz, 2H).

2-(2-Fluorophenyl)-1-(4-methylsulfanylphenyl)ethanone (49) was prepared according to method A starting from thioanisole (3.33 g) and 2-fluorophenylacetyl chloride. Crystallization from ethyl ether gave 3.99 g (57%) of **49**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.29 (s, 2H), 7.03−7.14 (m, 2H), 7.21−7.31 (m, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H).

2-(3-Fluorophenyl)-1-(4-methylsulfanylphenyl)ethanone (50) was prepared according to method A starting from thioanisole (3.80 g) and 3-fluorophenylacetyl chloride. Crystallization from hexane gave 1.39 g (16%) of **50**: ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 4.24 (s, 2H), 6.93−7.04 (m, 3H), 7.25−7.33 (m, 1H), 7.28 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H).

2-(4-Fluorophenyl)-1-(4-methylsulfanylphenyl)ethanone (51) was prepared according to method A starting from thioanisole (23.5 g) and 4-fluorophenylacetyl chloride. Crystallization from hexane gave 38.0 g (77%) of **51**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.21 (s, 2H), 6.97−7.04 (m, 2H), 7.18−7.28 (m, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Chlorophenyl)-1-(4-methylsulfanylphenyl)ethanone (52) was prepared according to method A starting from thioanisole (6.18 g) and 4-chlorophenylacetyl chloride. Crystallization from ethyl ether gave 10.7 g (78%) of **52**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.20 (s, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Bromophenyl)-1-(4-methylsulfanylphenyl)ethanone (53) was prepared according to method A starting from thioanisole (5.25 g) and 4-bromophenylacetyl chloride. Crystallization from ethyl ether gave 14.0 g (93%) of **53**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.20 (s, 2H), 7.11 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.44 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

1-(4-Methylsulfanylphenyl)-2-(4-trifluoromethylphenyl)ethanone (54) was prepared according to method A starting from thioanisole (9.62 g) and 4-trifluoromethylphenylacetyl chloride. Purification by flash chromatography, eluting with EtOAc/hexane (1:6), gave 1.86 g (8%) of **54**: ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 4.33 (s, 2H), 7.28 (d, J = 8.5 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H).

2-(4-Methylphenyl)-1-(4-methylsulfanylphenyl)ethanone (55) was prepared according to method A starting from thioanisole (23.0 g) and 4-methylphenylacetyl chloride. Crystallization from EtOAc/hexane gave 33.1 g (66%) of **55**: ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.52 (s, 3H), 4.20 (s, 2H), 7.14 (s, 4H), 7.25 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H).

2-(3,4-Dichlorophenyl)-1-(4-methylsulfanylphenyl)ethanone (56) was prepared according to method A starting from thioanisole (14.0 g) and 3,4-dichlorophenylacetyl chloride. Crystallization from ethyl ether gave 28.0 g (72%) of **56**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.20 (s, 2H), 7.10 (d, J = 8.5 Hz, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.40 (s, 1H), 7.92 (d, J = 8.5 Hz, 2H).

2-(2,4-Difluorophenyl)-1-(4-methylsulfanylphenyl)ethanone (57) was prepared according to method A starting from thioanisole (2.85 g) and 2,4-difluorophenylacetyl chloride. Crystallization from ethyl ether gave 5.10 g (80%) of **57**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.24 (s, 2H), 6.80−6.89 (m, 2H), 7.15−7.23 (m, 1H), 7.27 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H).

2-(4-Chloro-2-fluorophenyl)-1-(4-methylsulfanylphenyl)ethanone (58) was prepared according to method A starting from thioanisole (3.03 g) and 2-chloro-4-fluorophenylacetyl chloride. Crystallization from ethyl ether gave 5.20 g (72%) of **58**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.24 (s, 2H), 7.10−7.17 (m, 3H), 7.27 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H).

2-(2-Naphthyl)-1-(4-methylsulfanylphenyl)ethanone (59) was prepared according to method A starting from thioanisole (6.10 g) and 2-naphthylacetyl chloride. Crystallization from ethyl ether gave 12.9 g (90%) of **59**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 4.40 (s, 2H), 7.27−7.52 (m, 6H), 7.73 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 7.94 (d, J = 8.5 Hz, 2H).

1-(4-Methylsulfanylphenyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (60) was prepared according to method A starting from thioanisole (2.42 g) and (5,6,7,8-tetrahydronaphthalen-2-yl)acetyl chloride.[19] The title compound was obtained as a brown oil that was used in the next step without

further purification. ^{1}H NMR ($CDCl_3$) δ 1.72−1.76 (m, 4H), 2.49 (s, 3H), 2.68−2.73 (m, 4H), 4.13 (s, 2H), 6.88−6.97 (m, 3H), 7.21 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H).

3-Methyl-1-(4-methylsulfanylphenyl)butan-1-one (61) was prepared according to method A starting from thioanisole (5.25 g) and isobutyryl chloride. Crystallization from isopropyl ether gave 6.20 g (71%) of **61**: ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.3 Hz, 6H), 2.24−2.33 (m, 1H), 2.52 (s, 3H), 2.80 (d, J = 6.3 Hz, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H).

2-Cyclohexyl-1-(4-methylsulfanylphenyl)ethanone (62) was prepared according to method A starting from thioanisole (7.94 g) and cyclohexylacetyl chloride. Crystallization from isopropyl ether gave 14.9 g (94%) of **62**: ^{1}H NMR ($CDCl_3$) δ 0.95−1.33 (m, 5H), 1.65−1.76 (m, 5H), 1.87−2.00 (m, 1H), 2.52 (s, 3H), 2.79 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.85 (d, J = 8.5 Hz, 2H).

1-(4-Methylsulfanylphenyl)-3-phenylpropan-1-one (63) was prepared according to method A starting from thioanisole (7.56 g) and 3-phenylpropionyl chloride. Crystallization from ethyl ether gave 15.0 g (96%) of **63**: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 3.07 (t, J = 8.0 Hz, 2H), 3.25 (t, J = 8.0 Hz, 2H), 7.20−7.33 (m, 7H), 7.89 (d, J = 8.5 Hz, 2H).

General Procedure for the Synthesis of Intermediates 64−79. Method B. 1-(4-Methanesulfonylphenyl)-2-phenylethanone (64). To a cooled solution of 14.4 g (59.3 mmol) of **48** in 250 mL of CH_2Cl_2 and 50 mL of MeOH was added 35.2 g (71.2 mmol) of magnesium monoperoxyphthalate hexahydrate for 30 min. The mixture was stirred at room temperature overnight. The resulting suspension was poured into saturated $NaHCO_3$. The solid obtained was filtered, dried, and recrystallized from EtOH to give 8.76 g (57%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 4.30 (s, 2H), 7.25−7.38 (m, 5H), 8.07 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.5 Hz, 2H).

2-(2-Fluorophenyl)-1-(4-methanesulfonylphenyl)ethanone (65) was prepared according to method B starting from **49** (3.97 g). Crystallization from isopropyl ether gave 3.51 g (79%) of **65**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 4.36 (s, 2H), 7.06−7.15 (m, 2H), 7.23−7.34 (m, 2H), 8.07 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.5 Hz, 2H).

2-(3-Fluorophenyl)-1-(4-methanesulfonylphenyl)ethanone (66) was prepared according to method B starting from **50** (1.39 g). Crystallization from isopropyl ether gave 1.10 g (71%) of **66**: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 4.34 (s, 2H), 6.94−7.03 (m, 3H), 7.22−7.35 (m, 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H).

2-(4-Fluorophenyl)-1-(4-methanesulfonylphenyl)ethanone (67) was prepared according to method B starting from **51** (35.5 g). Recrystallization from isopropyl alcohol gave 25.0 g (63%) of **67**: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 4.29 (s, 2H), 7.03 (dd, $J_1 = J_{F-H}$ = 9.0 Hz, 2H), 7.22 (dd, $J_1 = J_{F-H}$ = 9.0 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H).

2-(4-Chlorophenyl)-1-(4-methanesulfonylphenyl)ethanone (68) was prepared according to method B starting from **52** (9.70 g). Crystallization from ethyl ether gave 7.40 g (68%) of **68**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 4.31 (s, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 8.05 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H).

2-(4-Bromophenyl)-1-(4-methanesulfonylphenyl)ethanone (69) was prepared according to method B starting from **53** (10.0 g). Crystallization from EtOAc gave 8.50 g (70%) of **69**: ^{1}H NMR (DMSO) δ 3.30 (s, 3H), 4.50 (s, 2H), 7.26 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H), 8.28 (d, J = 8.5 Hz, 2H).

1-(4-Methanesulfonylphenyl)-2-(4-trifluoromethylphenyl)ethanone (70) was prepared according to method B starting from **54** (1.86 g). Crystallization from ethyl ether gave 1.57 g (77%) of **70**: ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 4.41 (s, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 8.08 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H).

1-(4-Methanesulfonylphenyl)-2-(4-methylphenyl)ethanone (71) was prepared according to method B starting from **55** (7 g). Crystallization from ethyl ether gave 1.84 g (23%) of **71**: ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.07 (s, 3H), 4.26 (s, 2H), 7.12 (s, 4H), 8.03 (d, J = 8.5 Hz, 2H), 8.15 (d, J = 8.5 Hz, 2H).

2-(3,4-Dichlorophenyl)-1-(4-methanesulfonylphenyl)-ethanone (72) was prepared according to method B starting from **56** (28.0 g). Crystallization from ethyl ether gave 16.0 g (53%) of **72**: ^{1}H NMR (DMSO) δ 3.28 (s, 3H), 4.55 (s, 2H), 7.25 (d, J = 8.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 1H), 7.59 (s, 1H), 8.09 (d, J = 8.5 Hz, 2H), 8.2 (d, J = 8.5 Hz, 2H).

2-(2,4-Difluorophenyl)-1-(4-methanesulfonylphenyl)-ethanone (73) was prepared according to method B starting from **57** (5.33 g). Crystallization from ethyl ether gave 5.38 g (91%) of **73**: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 4.33 (s, 2H), 6.85−6.92 (m, 2H), 7.15−7.23 (m, 1H), 8.07 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H).

2-(4-Chloro-2-fluorophenyl)-1-(4-methanesulfonylphenyl)ethanone (74) was prepared according to method B starting from **58** (5.20 g). Crystallization from ethyl ether gave 5.00 g (87%) of **74**: ^{1}H NMR ($CDCl_3$) δ 3.12 (s, 3H), 4.37 (s, 2H), 7.13−7.20 (m, 3H), 8.11 (d, J = 8.5 Hz, 2H), 8.21 (d, J = 8.5 Hz, 2H).

2-(2-Naphthyl)-1-(4-methanesulfonylphenyl)ethanone (75) was prepared according to method B starting from **59** (12.9 g). Crystallization from ethyl ether gave 14.5 g (91%) of **75**: ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3H), 4.45 (s, 2H), 7.44−7.52 (m, 3H), 7.72 (s, 1H), 7.77−7.93 (m, 3H), 8.03 (d, J = 8.5 Hz, 2H), 8.19 (d, J = 8.5 Hz, 2H).

1-(4-Methanesulfonylphenyl)-2-(5,6,7,8-tetrahydronaphthalen-2-yl)ethanone (76) was prepared according to method B starting from **60** (6.10 g of crude material). The title compound was obtained (5.90 g, 92%) as a brown oil: ^{1}H NMR ($CDCl_3$) δ 1.77−1.80 (m, 4H), 2.70−2.75 (m, 4H), 3.08 (s, 3H), 4.27 (s, 2H), 6.93−7.04 (m, 3H), 8.03 (d, J = 8.5 Hz, 2H), 8.16 (d, J = 8.5 Hz, 2H).

3-Methyl-1-(4-methanesulfonylphenyl)butan-1-one (77) was prepared according to method B starting from **61** (6.10 g). Crystallization from isopropyl ether gave 4.28 g (61%) of **77**: ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.3 Hz, 6H), 2.25−2.35 (m, 1H), 2.88 (d, J = 6.3 Hz, 2H), 3.09 (s, 3H), 8.05 (d, J = 8.5 Hz, 2H), 8.12 (d, J = 8.5 Hz, 2H).

2-Cyclohexyl-1-(4-methanesulfonylphenyl)ethanone (78) was prepared according to method B starting from **62** (14.9 g). Crystallization from isopropyl ether gave 16.0 g (95%) of **78**: ^{1}H NMR ($CDCl_3$) δ 0.94−1.32 (m, 5H), 1.64−1.80 (m, 5H), 1.91−2.06 (m, 1H), 2.88 (d, J = 8.0 Hz, 2H), 3.11 (s, 3H), 8.05 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H).

1-(4-Methanesulfonylphenyl)-3-phenylpropan-1-one (79) was prepared according to method B starting from **63** (15.0 g). Crystallization from ethyl ether gave 14.4 g (85%) of **79**: ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 3.08 (t, J = 8.0 Hz, 2H), 3.36 (t, J = 8.0 Hz, 2H), 7.20−7.33 (m, 5H), 8.03 (d, J = 8.5 Hz, 2H), 8.11 (d, J = 8.5 Hz, 2H).

General Procedure for the Synthesis of Pyrones 1−16. Method C. 2-(4-Methanesulfonylphenyl)-6-methyl-3-phenylpyran-4-one (1). A solution of 40.0 g of polyphosphoric acid in 50 mL of acetic acid was heated at 140 °C. Then a suspension of 4.00 g (14.6 mmol) of **64** in 10 mL of acetic acid was added. The mixture was heated at 140 °C for 16 h. After cooling, the reaction mixture was poured into ice/water and extracted with EtOAc. The organic solution was dried, and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography, eluting with EtOAc/hexane (2:1), to give 3 g of crude **1**. Recrystallization from EtOH gave 1.00 g (20%) of the title compound: mp 185 °C; ^{1}H NMR (DMSO) δ 2.38 (s, 3H), 3.22 (s, 3H), 6.40 (s, 1H), 7.10−7.13 (m, 2H), 7.29−7.31 (m, 3H), 7.55 (d, J = 8.5 Hz, 2H), 7.86 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 99.4%. Anal. ($C_{19}H_{16}O_4S$) C, H, S.

3-(2-Fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (2) was prepared according to method C starting from **65** (3.50 g). Purification by flash chromatography, eluting with EtOAc/hexane (2:1), gave 2.96 g (69%) of **2**: mp 136−137 °C; ^{1}H NMR (DMSO) δ 2.40 (s, 3H), 3.04 (s, 3H), 6.36 (s, 1H), 6.99−7.05 (m, 1H), 7.10−7.20 (m, 2H), 7.29−7.37 (m, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.84 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 96.5%.

3-(3-Fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (3) was prepared according to method C starting from **66** (1.10 g). Purification by flash chromatography, eluting with EtOAc/hexane (2:1), gave 0.65 g (54%) of **3**: mp 182 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 3.22 (s, 3H), 6.41

(s, 1H), 6.88 (d, J = 7.9 Hz, 1 H), 7.03 (dt, J = 10.0, 2.0 Hz, 1H), 7.12 (td, J = 8.7, 2.0 Hz, 1H), 7.31 (td, J = 7.9, 6.4 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 99.3%.

3-(4-Fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (4) was prepared according to method C starting from **67** (1.00 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.50 g (41%) of **4**: mp 237 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 3.22 (s, 3H), 6.39 (s, 1H), 7.13−7.16 (m, 4H), 7.56 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 98.4%. Anal. ($C_{19}H_{15}FO_4S$) C, H, S.

3-(4-Chlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (5) was prepared according to method C starting from **68** (2.00 g). Recrystallization from EtOH gave 1.70 g (70%) of **5**: mp 182°C; ^{1}H NMR (DMSO) δ 2.38 (s, 3H), 3.24 (s, 3H), 6.41 (s, 1H), 7.15 (d, J = 8.5 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 98.6%. Anal. ($C_{19}H_{15}ClO_4S$) C, H, S.

3-(4-Bromophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (6) was prepared according to method C starting from **69** (8.5 g). Purification by flash chromatography, eluting with EtOAc/hexane (2:1), gave 1.03 g (12%) of **6**: mp 198 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 3.24 (s, 3H), 6.41 (s, 1H), 7.08 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 98.0%.

2-(4-Methanesulfonylphenyl)-6-methyl-3-(4-trifluoromethylphenyl)pyran-4-one (7) was prepared according to method C starting from **70** (1.57 g). Purification by flash chromatography, eluting with EtOAc/hexane (3:1), gave 0.70 g of the title compound. Recrystallization from ethanol gave 0.43 g (23%) of **7**: mp 170 °C; ^{1}H NMR (DMSO) δ 2.40 (s, 3H), 3.24 (s, 3H), 6.45 (s, 1H), 7.37 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 7.69 (d, J = 8.2 Hz, 2H), 7.90 (d, J = 8.2 Hz, 2H). HPLC purity (method 1): 99.2%. Anal. ($C_{20}H_{15}F_3O_4S$) C, H, S.

2-(4-Methanesulfonylphenyl)-6-methyl-3-(4-methylphenyl)pyran-4-one (8) was prepared according to method C starting from **71** (1.84 g). Purification by flash chromatography, eluting with EtOAc, gave 0.32 g (14%) of **8**: mp 205 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 2.39 (s, 3H), 3.04 (s, 3H), 6.34 (s, 1H), 7.02 (d, J = 8.0 Hz, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.2 Hz, 2H). HPLC purity (method 1): 95.6%.

3-(3,4-Dichlorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (9) was prepared according to method C starting from **72** (3.00 g). Purification by flash chromatography, eluting with EtOAc/hexane (2:1), gave 2.00 g (60%) of **9**: mp 160 °C; ^{1}H NMR (DMSO) δ 2.39 (s, 3H), 3.24 (s, 3H), 6.44 (s, 1H), 7.04 (d, J = 8.2 Hz, 1H), 7.49 (s, 1H), 7.55 (d, J = 8.2 Hz, 1H), 7.62 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 99.1%. Anal. ($C_{19}H_{14}Cl_2O_4S$) C, H, S.

3-(2,4-Difluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (10) was prepared according to method C starting from **73** (5.38 g). Recrystallization from EtOH gave 1.95 g (30%) of **10**: mp 208 °C; ^{1}H NMR ($CDCl_3$) δ 2.41 (s, 3H), 3.06 (s, 3H), 6.35 (s, 1H), 6.77 (td, J = 9.1, 2.4 Hz, 1H), 6.89 (td, J = 8.3, 1.7 Hz, 1H), 7.17 (dd, J = 8.3, 6.7 Hz, 1H), 7.52 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 99.0%.

3-(4-Chloro-2-fluorophenyl)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (11) was prepared according to method C starting from **74** (2.50 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.00 g (33%) of **11**: mp 171 °C; ^{1}H NMR (DMSO) δ 2.40 (s, 3H), 3.25 (s, 3H), 6.43 (s, 1H), 7.19−7.29 (m, 2H), 7.44 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 8.2 Hz, 2H), 7.95 (d, J = 8.2 Hz, 2H). HPLC purity (method 1): 95.5%.

2-(4-Methanesulfonylphenyl)-6-methyl-3-(naphthalen-2-yl)pyran-4-one (12) was prepared according to method C starting from **75** (14.5 g). Purification by flash chromatography, eluting with EtOAc/hexane (3:1), gave 1.10 g (6%) of **12**: mp 122−123 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.99 (s, 3H), 6.40 (s, 1H), 7.20 (d, J = 8.2 Hz, 1H), 7.42−7.52 (m, 4H), 7.69−7.83 (m, 6H). HPLC purity (method 1): 95.4%.

2-(4-Methanesulfonylphenyl)-6-methyl-3-(5,6,7,8-tetrahydronaphthalen-2-yl)pyran-4-one (13) was prepared according to method C starting from **76** (5.90 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.48 g (8%) of **13**: mp 103 °C; ^{1}H NMR (DMSO) δ 1.63−1.74 (m, 4H), 2.35 (s, 3H), 2.60−2.67 (m, 4H), 3.22 (s, 3H), 6.35 (s, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.84 (s, 1H), 6.93 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.87 (d, J = 8.2 Hz, 2H). HPLC purity (method 1): 95.0%.

3-Isopropyl-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (14) was prepared according to method C starting from **77** (3.50 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.22 g (5%) of **14**: mp 108 °C; ^{1}H NMR (DMSO) δ 1.22 (d, J = 6.3 Hz, 6H), 2.24 (s, 3H), 2.61 (h, J = 6.3 Hz, 1H), 3.31 (s, 3H), 6.20 (s, 1H), 7.82 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 99.3%.

3-Cyclohexyl-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (15) was prepared according to method C starting from **78** (16.0 g). Purification by flash chromatography, eluting with EtOAc/hexane (3:1), gave 2.3 g (12%) of **15**: mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 1.02−1.35 (m, 3H), 1.46−1.75 (m, 5H), 2.25 (s, 3H), 2.16−2.38 (m, 3H), 3.14 (s, 3H), 6.13 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 8.08 (d, J = 8.2 Hz, 2H). HPLC purity (method 1): 98.6%.

3-Benzyl-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (16) was prepared according to method C starting from **79** (7.00 g). Purification by flash chromatography, eluting with EtOAc/hexane (5:2), gave 1.80 g (21%) of **16**: mp 137 °C; ^{1}H NMR ($CDCl_3$) δ 2.33 (s, 3H), 3.08 (s, 3H), 3.81 (s, 2H), 6.27 (s, 1H), 7.04−7.06 (m, 2H), 7.13−7.27 (m, 3H), 7.63 (d, J = 8.0 Hz, 2H), 7.99 (d, J = 8.0 Hz, 2H). HPLC purity (method 1): 99.4%.

5.2. Synthesis of Pyrone 17 (Scheme 2). 1-(4-Fluorophenyl)-2-(4-methylsulfanylphenyl)ethanone (80). To a cooled solution of 32.6 g (0.162 mol) of 4-methylsulfanylphenylacetyl chloride and 33.3 g (0.346 mol) of fluorobenzene in 350 mL of carbon disulfide was added 48.5 g (0.364 mol) of aluminum trichloride in small portions. After being stirred at room temperature for 24 h, the mixture was poured into HCl/ice and extracted with CH_2Cl_2. The combined organic phase was washed with 2 N NaOH, dried, and evaporated. The resulting solid was recrystallized from hexane/$CHCl_3$ (95:5) to give 13.1 g (31%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 4.21 (s, 2H), 7.10−7.27 (m, 6H), 8.00−8.05 (m, 2H).

1-(4-Fluorophenyl)-2-(4-methanesulfonylphenyl)ethanone (81) was prepared according to method B starting from **80** (13.1 g). Crystallization from ethyl ether gave 12.8 g (87%) of **81**: ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 4.39 (s, 2H), 7.18 (dd, $J_1 = J_{F-H}$ = 9.0 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.92 (d, J = 8.5 Hz, 2H), 8.03−8.08 (m, 2H).

2-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)-6-methylpyran-4-one (17) was prepared according to method C starting from **81** (1.00 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.40 g (33%) of **17**: mp 193 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 3.20 (s, 3H), 6.39 (s, 1H), 7.19 (dd, $J_1 = J_{F-H}$ = 9.0 Hz, 2H), 7.36−7.39 (m, 2H), 7.36 (d, J = 8.2 Hz, 2H), 7.83 (d, J = 8.2 Hz, 2H). HPLC purity: 97.3%. Anal. ($C_{19}H_{15}FO_4S$) C, H, S.

5.3. Synthesis of Pyrones 18 and 19 (Scheme 3). 4-Sulfamoylbenzoic Acid Ethyl Ester (82). To a suspension of 99.0 g (0.492 mol) of 4-sulfamoylbenzoic acid in 990 mL of EtOH was added dropwise 990 mL of EtOH saturated with HCl(g). The mixture was stirred at room temperature overnight. The insoluble starting material was filtered, and the solvent was removed under reduced pressure. The resulting solid was washed with isopropyl ether, filtered, and dried to give 110.5 g (98%) of the title compound: ^{1}H NMR (DMSO) δ 1.17 (t, J = 7.5 Hz, 3H), 4.24 (q, J = 7.5 Hz, 2H), 7.51 (s, 2H), 7.93 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H).

4-(Dibenzylsulfamoyl)benzoic Acid Ethyl Ester (83). To a suspension of 110.5 g (0.48 mol) of **82** and 199 g (1.44 mol) of K_2CO_3 in 400 mL of acetone was added dropwise a

solution of 164 g (0.96 mol) of benzyl chloride in 100 mL of acetone. The mixture was refluxed for 5 h. After the mixture was cooled, the solvent was evaporated, the resulting solid was suspended in water, and the sample was extracted with CH_2Cl_2. The combined organic layer was washed with water dried, and the solvent was removed under reduced pressure. The resulting solid was washed with hexane, filtered, and dried to give 176.4 g (89%) of **83**: ^{1}H NMR ($CDCl_3$) δ 1.42 (t, J = 7.5 Hz, 3H), 4.35 (s, 4H), 4.43 (q, J = 7.5 Hz, 2H), 7.04−7.06 (m, 4H), 7.20−7.24 (m, 6H), 7.88 (d, J = 8.5 Hz, 2H), 8.13 (d, J = 8.5 Hz, 2H).

4-(Dibenzylsulfamoyl)benzoic Acid (84). A suspension of 176.4 g (0.43 mol) of **83** and 315 mL of 2 N NaOH in 900 mL of EtOH was refluxed for 1 h. The mixture was cooled, and the solvent was removed under reduced pressure. The residue was suspended in water and the mixture was acidified with HCl(conc). The resulting solid was filtered, washed with water, and dried to yield 162.3 g (99%) of **84**: ^{1}H NMR (DMSO) δ 4.29 (s, 4H), 7.06−7.09 (m, 4H), 7.17−7.24 (m, 6H), 7.78 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.5 Hz, 2H).

4-Dibenzylsulfamoyl-*N*-methoxy-*N*-methylbenzamide (85). A solution of 24 g (63 mmol) of **84** in 50 mL of thionyl chloride was refluxed for 2.5 h, and the excess thionyl chloride was removed under reduced pressure. The resulting oil was dissolved in 150 mL of CH_2Cl_2 and added slowly to a solution of 7.37 g (75.6 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride and 21.8 mL (151 mmol) of triethylamine in 150 mL of CH_2Cl_2. The mixture was stirred at room temperature for 16 h. The insoluble material was filtered off, and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography, eluting with EtOAc/hexane (1:1), to give 22 g (85%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 3H), 3.57 (s, 3H), 4.37 (s, 4H), 7.05−7.07 (m, 4H), 7.20−7.29 (m, 6H), 7.80 (d, J = 8.5 Hz, 2H), 7.88 (d, J = 8.5 Hz, 2H).

General Procedure for the Synthesis of Intermediates 86 and 87. Method D. *N*,*N*-Dibenzyl-4-phenylacetylbenzenesulfonamide (86). To a suspension of 2 g (82.4 mmol) of magnesium in 20 mL of anhydrous THF was slowly added a solution of 10.4 g (82.4 mmol) of benzyl chloride in 100 mL of anhydrous THF. When the reaction was completed, a solution of 7.00 g (16.5 mmol) of **85** in 50 mL of anhydrous THF was slowly added while the temperature was maintained at 0 °C. After being stirred at the same temperature for half an hour, the reaction mixture was poured into a saturated ammonium chloride solution and extracted with ethyl ether and the organic extracts were dried. The solvent was removed under reduced pressure and the residual oil was purified by flash chromatography, eluting with hexane/EtOAc (1:3), to give 6.80 g (90%) of **86**: ^{1}H NMR ($CDCl_3$) δ 4.31 (s, 2H), 4.34 (s, 4H), 7.00−7.06 (m, 4H), 7.17−7.20 (m, 6H), 7.25−7.37 (m, 5H), 7.91 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H).

***N*,*N*-Dibenzyl-4-[2-(4-fluorophenyl)acetyl]benzenesulfonamide (87)** was prepared according to method D starting from **85** (10.75 g) and 4-fluorobenzyl chloride. Crystallization from ethyl ether/pentane (1:2) gave 5.60 g (47%) of **87**: ^{1}H NMR ($CDCl_3$) δ 4.34 (s, 4H), 4.51 (s, 2H), 7.07−7.12 (m, 4H), 7.18−7.23 (m, 8H), 7.31−7.36 (m, 2H), 8.04 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H).

General Procedure for the Synthesis of Pyrones 18 and 19. Method E. 4-(6-Methyl-4-oxo-3-phenyl-4*H*-pyran-2-yl)benzenesulfonamide (18). A solution of 94.0 g of polyphosphoric acid in 120 mL of acetic acid was heated at 140 °C. Then a suspension of 9.40 g (20.7 mmol) of **86** in 20 mL of acetic acid was added. The mixture was heated at 140 °C for 16 h. After cooling, the reaction mixture was poured into ice/water and extracted with EtOAc. The organic layer was dried, and the solvent was removed under reduced pressure. To the residual oil was added 38 mL of concentrated sulfuric acid, and the mixture was stirred at 0 °C for 10 min, was stirred an additional 60 min at room temperature, and was poured into ice/water. The precipitated solid was collected by filtration. Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.53 g (22%) of **18**: mp 218 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 6.38 (s, 1H), 7.09−7.12 (m, 2H), 7.28−7.30 (m, 3H), 7.44 (s, 2H), 7.47 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H). HPLC purity: 98.6%. Anal. ($C_{18}H_{15}NO_4S$) C, H, N, S.

4-[3-(4-Fluorophenyl)-6-methyl-4-oxo-4*H*-pyran-2-yl]benzenesulfonamide (19) was prepared according to method F starting from **87** (5.50 g). Purification by flash chromatography, eluting with CH_2Cl_2/EtOAc/AcOH (78:10:1), gave 1.01 g (26%) of **19**: mp 247 °C; ^{1}H NMR (DMSO) δ 2.37 (s, 3H), 6.39 (s, 1H), 7.15 (d, J = 7.5 Hz, 4H), 7.46 (s, 2H), 7.49 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 8.5 Hz, 2H). HPLC purity: 98.2%. Anal. ($C_{18}H_{14}NFO_4S$) C, H, N, S.

5.4. Synthesis of Pyrones 20−40 (Scheme 4). General Procedure for the Synthesis of Intermediates 88−108. Method F. 2-(4-Fluorophenoxy)-1-(4-methylsulfanylphenyl)ethanone (88). To a solution of 0.7 g (6.1 mmol) of 4-fluorophenol in 5 mL of CH_2Cl_2 and 1.28 g (9.2 mmol) of K_2CO_3 in 4 mL of water was added 0.1 g (0.3 mmol) of tetrabutylammonium hydrogen sulfate and a solution of 1.5 g (6.1 mmol) of 2-bromo-1-(4-methylsulfanylphenyl)ethanone[16] in 5 mL of CH_2Cl_2. The mixture was stirred at room temperature for 16 h. Water was added, the organic phase was decanted, and the basic phase was extracted with CH_2Cl_2. The organic solution was dried, and the solvent was removed under reduced pressure. The resulting solid was washed with ethyl ether to yield 1.1 g (65%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 2.52 (s, 3H), 5.17 (s, 2H), 6.85−7.00 (m, 4H), 7.27 (d, J = 8.5 Hz, 2H), 7.89 (d, J = 8.5 Hz, 2H).

2-(4-Chlorophenoxy)-1-(4-methylsulfanylphenyl)ethanone (89) was prepared according to method F starting from 4-chlorophenol (21 g). Crystallization from ethyl ether gave 42.7 g (90%) of **89**: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.20 (s, 2H), 6.88 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(2-Bromophenoxy)-1-(4-methylsulfanylphenyl)ethanone (90) was prepared according to method F starting from 2-bromophenol (4.9 g). Crystallization from ethyl ether gave 7.45 g (77%) of **90**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.30 (s, 2H), 6.87 (m, 2H), 7.20 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 1H), 7.97 (d, J = 8.5 Hz, 2H).

2-(3-Bromophenoxy)-1-(4-methylsulfanylphenyl)ethanone (91) was prepared according to method F starting from 3-bromophenol (5.3 g). Crystallization from ethyl ether gave 6.7 g (65%) of **91**: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.23 (s, 2H), 6.88 (m, 1H), 7.15 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H).

2-(4-Bromophenoxy)-1-(4-methylsulfanylphenyl)ethanone (92) was prepared according to method F starting from 4-bromophenol (4.87 g). Crystallization from ethyl ether gave 7.86 g (83%) of **92**: ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 5.20 (s, 2H), 6.80 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.40 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Iodophenoxy)-1-(4-methylsulfanylphenyl)ethanone (93) was prepared according to method F starting from 4-iodophenol (1.8 g). Crystallization from ethyl ether and EtOAc gave 2.5 g (81%) of **93**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.20 (s, 2H), 6.73 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.60 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Trifluoromethylphenoxy)-1-(4-methylsulfanylphenyl)ethanone (94) was prepared according to method F starting from 4-trifluoromethylphenol (1.3 g). Crystallization from ethyl ether gave 2.6 g (99%) of **94**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.33 (s, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.57 (d, J = 8.5 Hz, 2H), 7.93 (d, J = 8.5 Hz, 2H).

2-(4-Pentafluoroethylphenoxy)-1-(4-methylsulfanylphenyl)ethanone (95) was prepared according to method F starting from 4-pentafluoroethylphenol (0.84 g) and 2-bromo-1-(4-methylsulfanylphenyl)ethanone. Crystallization from ethyl ether gave 1.5 g (100%) of **95**: MS (M^+), *m*/*z*: 376.

2-(4-Trifluoromethoxyphenoxy)-1-(4-methylsulfanylphenyl)ethanone (96) was prepared according to method F starting from 4-trifluoromethoxyphenol (1.4 g). Crystallization from ethyl ether gave 2.37 g (86%) of **96**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.20 (s, 2H), 6.93 (d, J = 8.5 Hz, 2H), 7.17 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Nitrophenoxy)-1-(4-methylsulfanylphenyl)ethanone (97) was prepared according to method F starting from 4-nitrophenol (2.1 g). Crystallization from ethyl ether gave 4.6 g (100%) of **97**: ^{1}H NMR (DMSO) δ 2.60 (s, 3H), 5.80 (s, 2H), 7.20 (d, J = 8.5 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H), 8.20 (d, J = 8.5 Hz, 2H).

4-[2-(4-Methylsulfanylphenyl)-2-oxoethoxy]benzoic acid methyl ester (98) was prepared according to method F starting from 4-hydroxybenzoic acid methyl ester (2.2 g). Crystallization from ethyl ether/EtOAc gave 2.7 g (59%) of **98**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.90 (s, 3H), 5.30 (s, 2H), 6.97 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.5 Hz, 2H).

2-(2,4-Difluorophenoxy)-1-(4-methylsulfanylphenyl)-ethanone (99) was prepared according to method F starting from 2,4-difluorophenol (18.6 g). Crystallization from ethyl ether gave 38.6 g (92%) of **99**: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.28 (s, 2H), 6.73−7.00 (m, 3H), 7.28 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(3,4-Difluorophenoxy)-1-(4-methylsulfanylphenyl)-ethanone (100) was prepared according to method F starting from 3,4-difluorophenol (3.5 g). Crystallization from ethyl ether gave 3.3 g (44%) of **100**: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.20 (s, 2H), 6.63 (m, 1H), 6.78 (m, 1H), 7.05 (m, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(3,4-Dichlorophenoxy)-1-(4-methylsulfanylphenyl)-ethanone (101) was prepared according to method F starting from 3,4-dichlorophenol (4.57 g). Crystallization from ethyl ether gave 9.2 g (100%) of **101**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.20 (s, 2H), 6.80 (d, J = 8.5 Hz, 1H), 7.03 (s, 1H), 7.30 (m, 3H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Chloro-2-fluorophenoxy)-1-(4-methylsulfanylphenyl)ethanone (102) was prepared according to method F starting from 4-chloro-2-fluorophenol (0.47 g). Crystallization from pentane/ethyl ether (4:1) gave 0.63 g (62%) of **102**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.30 (s, 2H), 6.83−7.17 (m, 3H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Bromo-2-fluorophenoxy)-1-(4-methylsulfanylphenyl)ethanone (103) was prepared according to method F starting from 4-bromo-2-fluorophenol (5.1 g). Crystallization from ethyl ether gave 6.8 g (78%) of **103**: ^{1}H NMR ($CDCl_3$) δ 2.55 (s, 3H), 5.30 (s, 2H), 6.83 (dd, $J_{HH} = J_{HF}$ = 5.0, 1H), 7.15 (m, 1H), 7.25−7.33 (m, 3H), 7.90 (d, J = 8.5 Hz, 2H).

2-(4-Bromo-2-chlorophenoxy)-1-(4-methylsulfanylphenyl)ethanone (104) was prepared according to method F starting from 4-bromo-2-chlorophenol (1.7 g). Crystallization from ethyl ether gave 2.6 g (87%) of **104**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 5.27 (s, 2H), 6.73 (d, J = 8.5 Hz, 2H), 7.27 (m, 3H), 7.53 (s, 1H), 7.93 (d, J = 8.5 Hz, 2H).

2-(4-Fluoro-2-methylphenoxy)-1-(4-methylsulfanylphenyl)ethanone (105) was prepared according to method F starting from 4-fluoro-2-methylphenol (5.8 g). Crystallization from ethyl ether gave 12.1 g (91%) of **105**: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.55 (s, 3H), 5.20 (s, 2H), 6.65−6.90 (m, 3H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(2-Chloro-4-methylphenoxy)-1-(4-methylsulfanylphenyl)ethanone (106) was prepared according to method F starting from 2-chloro-4-methylphenol (5.4 g). Crystallization from ethyl ether gave 10.4 g (96%) of **106**: ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.55 (s, 3H), 5.25 (s, 2H), 6.78 (d, J = 8.7 Hz, 1H), 6.95 (d, J = 8.7 Hz, 1H), 7.20 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.95 (d, J = 8.5 Hz, 2H).

2-(4-Chloro-2-methylphenoxy)-1-(4-methylsulfanylphenyl)ethanone (107) was prepared according to method F starting from 4-chloro-2-methylphenol (3.5 g). Crystallization from ethyl ether gave 6.35 g (84%) of **107**: ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.55 (s, 3H), 5.20 (s, 2H), 6.65 (d, J = 8.7 Hz, 1H), 7.05 (d, J = 8.7 Hz, 1H), 7.15 (s, 1H), 7.30 (d, J = 8.5 Hz, 2H), 7.90 (d, J = 8.5 Hz, 2H).

2-(2-Chloro-4-methoxyphenoxy)-1-(4-methylsulfanylphenyl)ethanone (108) was prepared according to method F starting from 2-chloro-4-methoxyphenol (1.3 g). Crystallization from hexane/ethyl ether gave 1.88 g (73%) of **108**: ^{1}H NMR ($CDCl_3$) δ 2.53 (s, 3H), 3.73 (s, 3H), 5.20 (s, 2H), 6.73−6.97 (m, 3H), 7.30 (d, J = 8.5 Hz, 2H), 7.97 (d, J = 8.5 Hz, 2H).

General Procedure for the Synthesis of Intermediates 109−112. Method B. 2-(4-Fluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (109) was prepared according to method B starting from **88** (1.10 g). Crystallization from ethyl ether gave 0.75 g (60%) of **109**: ^{1}H NMR (DMSO) δ 3.32 (s, 3H), 5.62 (s, 2H), 7.01−7.04 (m, 2H), 7.05−7.17 (m, 2H), 8.13 (d, J = 8.0 Hz, 2H), 8.25 (d, J = 8.0 Hz, 2H).

2-(4-Bromophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (110) was prepared according to method B starting from **92** (7.86 g). Crystallization from ethyl ether gave 7.55 g (88%) of **110**: ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 3H), 5.66 (s, 2H), 7.00 (d, J = 9.0 Hz, 2H), 7.46 (d, J = 9.0 Hz, 2H), 8.12 (d, J = 9.0 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H).

2-(2,4-Difluorophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (111) was prepared according to method B starting from **99** (6.60 g). Crystallization from ethyl ether gave 4.97 g (65%) of **111**: ^{1}H NMR (DMSO) δ 3.31 (s, 3H), 5.72 (s, 2H), 6.93−7.05 (m, 1H), 7.15−7.36 (m, 2H), 8.12 (d, J = 8.5 Hz, 2H), 8.22 (d, J = 8.5 Hz, 2H).

2-(3,4-Difluorophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (112) was prepared according to method B starting from **100** (3.30 g). Crystallization from ethyl ether gave 2.67 g (73%) of **112**: ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 5.26 (s, 2H), 6.64−6.68 (m, 1H), 6.76−6.81 (m, 1H), 7.03−7.14 (m, 1H), 8.10 (d, J = 8.0 Hz, 2H), 8.16 (d, J = 8.0 Hz, 2H).

General Procedure for the Synthesis of Intermediates 113−129. Method G. 2-(4-Chlorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (113). To a cooled solution of 42.7 g (0.146 mol) of **89** in 600 mL of acetone was added a solution of 164.4 g (0.267 mol) of Oxone in 600 mL of water. The mixture was stirred at room temperature overnight and diluted with 600 mL of water. The resulting solid was filtered off, washed with water, and dried to yield 39.0 g (82%) of the title compound: ^{1}H NMR (DMSO) δ 3.30 (s, 3H), 5.65 (s, 2H), 7.03 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 8.12 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H).

2-(2-Bromophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (114) was prepared according to method G starting from **90** (7.40 g). Crystallization from water gave 7.60 g (94%) of **114**: ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 3H), 5.30 (s, 2H), 6.80−6.94 (m, 2H), 7.20−7.26 (m, 1H), 7.53 (d, J = 7.5 Hz, 1H), 8.08 (d, J = 9.0 Hz, 2H), 8.23 (d, J = 9.0 Hz, 2H).

2-(3-Bromophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (115) was prepared according to method G starting from **91** (6.69 g). Crystallization from water gave 6.48 g (88%) of **115**: ^{1}H NMR (DMSO) δ 3.33 (s, 3H), 5.72 (s, 2H), 7.03−7.06 (m, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.32 (s, 1H), 8.13 (d, J = 8.0 Hz, 2H), 8.24 (d, J = 8.0 Hz, 2H).

2-(4-Iodophenoxy)-1-(4-methanesulfonylphenyl)ethanone (116) was prepared according to method G starting from **93** (2.50 g). Crystallization from water gave 2.80 g (100%) of **116**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 5.24 (s, 2H), 6.71 (d, J = 9.0 Hz, 1H), 7.60 (d, J = 9.0 Hz, 1H), 8.09 (d, J = 8.0 Hz, 2H), 8.18 (d, J = 8.0 Hz, 2H).

2-(4-Trifluoromethylphenoxy)-1-(4-methanesulfonylphenyl)ethanone (117) was prepared according to method G starting from **94** (2.88 g). Crystallization from ethyl ether gave 1.52 g (48%) of **117**: ^{1}H NMR ($CDCl_3$) δ 3.10 (s, 3H), 5.34 (s, 2H), 7.00 (d, J = 8.5 Hz, 2H), 7.56 (d, J = 8.5 Hz, 2H), 8.10 (d, J = 8.5 Hz, 2H), 8.17 (d, J = 8.5 Hz, 2H).

2-(4-Pentafluoroethylphenoxy)-1-(4-methanesulfonylphenyl)ethanone (118) was prepared according to method G starting from **95** (1.69 g). Purification by flash chromatography, eluting with EtOAc/hexane (2:3), gave 0.23 g (14%) of **118**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 5.33 (s, 2H), 7.03 (d, J = 9.0 Hz, 2H), 7.55 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.20 (d, J = 8.0 Hz, 2H).

2-(4-Trifluoromethoxyphenoxy)-1-(4-methanesulfonylphenyl)ethanone (119) was prepared according to method G starting from **96** (2.37 g). Crystallization from water gave 2.74 g (100%) of **119**: ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 5.26 (s, 2H), 6.92 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.20 (d, J = 8.0 Hz, 2H).

2-(4-Nitrophenoxy)-1-(4-methanesulfonylphenyl)ethanone (120) was prepared according to method G starting from

97 (4.60 g). Crystallization from water gave 3.70 g (74%) of **120**: ^{1}H NMR (DMSO) δ 3.35 (s, 3H), 5.89 (s, 2H), 7.26 (d, J = 9.0 Hz, 2H), 8.11−8.27 (m, 6H).

4-[2-(4-Methanesulfonylphenyl)-2-oxoethoxy]benzoic acid methyl ester (121) was prepared according to method G starting from **98** (2.67 g). Crystallization from water gave 2.38 g (81%) of **121**: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.90 (s, 3H), 5.35 (s, 2H), 6.98 (d, J = 8.0 Hz, 2H), 8.02 (d, J = 8.0 Hz, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.20 (d, J = 8.0 Hz, 2H).

2-(3,4-Dichlorophenoxy)-1-(4-methanesulfonylphenyl)-ethanone (122) was prepared according to method G starting from **100** (8.00 g). Crystallization from ethyl ether gave 7.28 g (83%) of **122**: ^{1}H NMR ($CDCl_3$) δ 3.09 (s, 3H), 5.24 (s, 2H), 6.82 (d, J = 9.0 Hz, 1H), 7.01 (s, 1H), 7.34 (d, J = 9.0 Hz, 1H), 8.07 (d, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H).

2-(4-Chloro-2-fluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (123) was prepared according to method G starting from **102** (0.63 g). Crystallization from water gave 0.58 g (84%) of **123**: ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H), 5.33 (s, 2H), 6.92 (t, J_{F-H} = 13.0 Hz, 1H), 7.00−7.20 (m, 2H), 8.11 (d, J = 8.0 Hz, 2H), 8.18 (d, J = 8.0 Hz, 2H).

2-(4-Bromo-2-fluorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (124) was prepared according to method G starting from **103** (6.80 g). Crystallization from water gave 7.60 g (100%) of **124**: ^{1}H NMR (DMSO) δ 3.32 (s, 3H), 5.80 (s, 2H), 7.10 (t, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 8.13 (d, J = 9.0 Hz, 2H), 8.24 (d, J = 9.0 Hz, 2H).

2-(4-Bromo-2-chlorophenoxy)-1-(4-methanesulfonylphenyl)ethanone (125) was prepared according to method G starting from **104** (2.59 g). Crystallization from water gave 2.18 g (78%) of **125**: ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 5.32 (s, 2H), 6.77 (d, J = 9.0 Hz, 1H), 7.32 (d, J = 9.0 Hz, 1H), 7.56 (s, 1H), 8.12 (d, J = 7.5 Hz, 2H), 8.24 (d, J = 7.5 Hz, 2H).

2-(4-Fluoro-2-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone (126) was prepared according to method G starting from **105** (12.1 g). Crystallization from water gave 11.2 g (83%) of **126**: ^{1}H NMR (DMSO) δ 2.22 (s, 3H), 3.30 (s, 3H), 5.63 (s, 2H), 6.89−7.06 (m, 3H), 8.08 (d, J = 8.0 Hz, 2H), 8.21 (d, J = 8.0 Hz, 2H).

2-(2-Chloro-4-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone (127) was prepared according to method G starting from **106** (10.4 g). Crystallization from water gave 10.0 g (88%) of **127**: ^{1}H NMR (DMSO) δ 2.23 (s, 1H), 3.32 (s, 3H), 5.74 (s, 2H), 7.02−7.04 (m, 2H), 7.24 (s, 1H), 8.12 (d, J = 8.0 Hz, 2H), 8.22 (d, J = 8.0 Hz, 2H).

2-(4-Chloro-2-methylphenoxy)-1-(4-methanesulfonylphenyl)ethanone (128) was prepared according to method G starting from **107** (6.27 g). Crystallization from water gave 6.40 g (92%) of **128**: ^{1}H NMR (DMSO) δ 2.23 (s, 3H), 3.31 (s, 3H), 5.68 (s, 2H), 6.96 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.5 Hz, 1H), 7.25 (s, 1H), 8.12 (d, J = 8.5 Hz, 2H), 8.24 (d, J = 8.5 Hz, 2H).

2-(2-Chloro-4-methoxyphenoxy)-1-(4-methanesulfonylphenyl)ethanone (129) was prepared according to method G starting from **108** (1.88 g). Crystallization from water gave 2.00 g (97%) of **129**: ^{1}H NMR ($CDCl_3$) δ 3.08 (s, 3H), 3.78 (s, 3H), 5.24 (s, 2H), 6.71−7.00 (m, 3H), 8.08 (d, J = 8.0 Hz, 2H), 8.23 (d, J = 8.0 Hz, 2H).

General Procedure for the Synthesis of Pyrones 20−40. 3-(4-Fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (20). Method H. A solution of 7.50 g of polyphosphoric acid in 9 mL of acetic acid was heated at 120 °C. Then a suspension of 0.75 g (2.4 mmol) of **109** in 2 mL of acetic acid was added. The mixture was heated at 120 °C for 4 h. After cooling, the reaction mixture was poured into ice/water and extracted with EtOAc. The organic solution was dried, and the solvent was removed under reduced pressure. The residual oil was purified by flash chromatography, eluting with EtOAc/hexane (1:1), to give 0.26 g (11%) of the title compound.

Method I. A solution of 82 g of polyphosphoric acid in 11.5 mL of acetic anhydride was heated to 100 °C during 10 min with mechanical stirring. Then the mixture was allowed to cool to 30 °C and 8.97 g of compound **109** were added in portions. Then the reaction mixture was heated to 100 °C for 4 h with stirring. After cooling, the reaction mixture was poured into ice/water and extracted with EtOAc. The organic layer was washed with saturated sodium bicarbonate, water, and brine, dried, and evaporated to give a residue that was purified by flash chromatography, eluting with hexane/EtOAc (1:3), to give 2.28 g (21%) of the title compound: mp 197 °C; ^{1}H NMR (DMSO) δ 2.43 (s, 3H), 3.26 (s, 3H), 6.47 (s, 1H), 6.98−7.04 (m, 2H), 7.09−7.15 (m, 2H), 8.07 (s, 4H). HPLC purity (method 1): 99.3%. Anal. ($C_{19}H_{15}FO_5S$) H, S. C: calcd, 60.37; found, 60.96.

3-(4-Chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (21) was prepared according to method H starting from **113** (2.7 g). Purification by flash chromatography with silica gel and hexane/EtOAc (2:3) as eluent gave 0.42 g (13%) of **21** as an off-white solid: mp 204 °C; ^{1}H NMR (DMSO) δ 2.44 (s, 3H), 3.26 (s, 3H), 6.48 (s, 1H), 7.20 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 9.0 Hz, 2H), 8.06 (s, 4H). HPLC purity (method 1): 99.1%. Anal. ($C_{19}H_{15}ClO_5S$) C, H, S.

3-(2-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (22) was prepared according to method I starting from **114** (2.25 g). Purification by flash chromatography, eluting with EtOAc, gave 0.87 g (33%) of **22**: mp 197−199 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.11 (s, 3H), 6.43 (s, 1H), 6.67 (d, J = 7.5 Hz, 1H), 6.92 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 7.5 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.18 (d, J = 9.0 Hz, 2H). HPLC purity (method 1): 98.7%.

3-(3-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (23) was prepared according to method I starting from **115** (7.24 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:3), gave 1.12 g (15%) of **23**: ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.09 (s, 3H), 6.40 (s, 1H), 6.91−6.93 (m, 1H), 7.08 (s, 1H), 7.15−7.20 (m, 2H), 8.03 (d, J = 8.5 Hz, 2H), 8.07 (d, J = 8.5 Hz, 2H). HPLC purity (method 1): 96.3%.

3-(4-Bromophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (24) was prepared according to method I starting from **110** (5.3 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:5), gave 1.7 g (27%) of **24**: mp 188 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.06 (s, 3H), 6.36 (s, 1H) 6.89 (d, J = 9.0 Hz, 2H), 7.20 (d, J = 9.0 Hz, 2H), 8.00 (d, J = 9.0 Hz, 2H), 8.07 (d, J = 9.0 Hz, 2H). HPLC purity (method 1): 99.4%.

3-(4-Iodophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (25) was prepared according to method I starting from **116** (2.8 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:2), gave 0.43 g (14%) of **25**: mp 223−226 °C; ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 3.07 (s, 3H), 6.36 (s, 1H), 6.73 (d, J = 8.9 Hz, 2H), 7.57 (d, J = 8.9 Hz, 2H), 8.00 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H). HPLC purity (method 1): 97.3%.

3-(4-Trifluoromethylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (26) was prepared according to method I starting from **117** (1.53 g). Purification by flash chromatography, eluting with EtOAc, gave 0.39 g (22%) of **26**: mp 206−208 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.07 (s, 3H), 6.38 (s, 1H), 7.03 (d, J = 8.4 Hz, 2H), 7.55 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.7 Hz, 2H), 8.06 (d, J = 8.7 Hz, 2H). HPLC purity (method 1): 98.9%.

3-(4-Pentafluoroethylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (27) was prepared according to method I starting from **118** (0.35 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:5), gave 0.05 g (12%) of **27**: mp 162−163 °C; ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.07 (s, 3H), 6.39 (s, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.52 (d, J = 8.4 Hz, 2H), 8.04 (m, 4H). HPLC purity (method 1): 95.0%.

3-(4-Trifluoromethoxyphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (28) was prepared according to method I starting from **119** (2.74 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:5), gave 0.24 g (8%) of **28**: mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.95 (d, J = 9.3 Hz, 2H), 7.20 (d, J = 9.3 Hz, 2H), 8.02 (d, J = 9.2 Hz, 2H), 8.08 (d, J = 9.2 Hz, 2H). HPLC purity (method 1): 96.2%.

3-(4-Nitrophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (29) was prepared according to method I starting from **120** (3.70 g). Purification by flash chromatog-

raphy, eluting with hexane/EtOAc (3:7), gave 1.46 g (33%) of **29**: mp 252°C; ^{1}H NMR (DMSO) δ 2.46 (s, 3H), 3.26 (s, 3H), 6.54 (s, 1H), 7.25 (dd, J = 6.9, 2.1 Hz, 2H), 8.06 (m, 4H), 8.20 (dd, J = 6.9, 2.1 Hz, 2H). HPLC purity (method 1): 99.4%.

4-[2-(4-Methanesulfonylphenyl)-6-methyl-4-oxo-4*H*-pyran-3-yloxy]benzoic acid methyl ester (30) was prepared according to method I starting from **121** (2.38 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:1), gave 0.8 g (28%) of **30**: mp 219 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.07 (s, 3H), 3.88 (s, 3H), 6.39 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.98−8.07 (m, 6H). HPLC purity (method 1): 99.2%.

3-(2,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (31) was prepared according to method H starting from **111** (18.5 g). Purification by flash chromatography with silica gel, eluting with and ethyl hexane/EtOAc (1:1), gave 9.96 g (22%) of **31**: mp 196−197 °C; ^{1}H NMR (DMSO) δ 2.44 (s, 3H), 3.26 (s, 3H), 6.48 (s, 1H), 6.89−6.98 (m, 1H), 7.04−7.14 (m, 1H), 7.34−7.44 (m, 1H), 8.09 (s, 4H). HPLC purity (method 1): 99.5%. Anal. ($C_{19}H_{14}F_2O_5S$) C, H, S.

3-(3,4-Difluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (32) was prepared according to method H starting from **112** (2.68 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:1), gave 0.38 g (12%) of **32**: mp 194 °C; ^{1}H NMR (DMSO) δ 2.42 (s, 3H), 3.26 (s, 3H), 6.48 (s, 1H), 6.86 (m, 1H), 7.24 (m, 1H), 7.36 (dd, J = 18.0, 10.8 Hz, 1H), 8.05 (m, 4H). HPLC purity (method 1): 98.9%.

3-(3,4-Dichlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (33) was prepared according to method H starting from **122** (4.9 g). Purification by flash chromatography, eluting with hexane/EtOAc (3:2), gave 0.30 g (5%) of **33**: mp 177 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.28 (s, 3H), 6.48 (s, 1H), 7.07 (m, 1H), 7.40 (s, 1H), 7.56 (d, J = 10.8 Hz, 1H), 8.08 (m, 4H). HPLC purity (method 1): 95.0%.

3-(4-Chloro-2-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (34) was prepared according to method I starting from **123** (0.58 g). Purification by flash chromatography, eluting with hexane/EtOAc (2/5), gave 0.23 g (34%) of **34**: mp 188−189 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.09 (s, 3H), 6.35 (s, 1H), 6.80 (dd, $J_{HH} = J_{HF}$ = 8.7 Hz, 1H), 6.97 (m, 1H), 7.15 (d, J = 12.6 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 8.11 (d, J = 8.7 Hz, 2H). HPLC purity (method 1): 99.6%. Anal. ($C_{19}H_{14}FClO_5S$) C, H, S.

3-(4-Bromo-2-fluorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (35) was prepared according to method I starting from **124** (2.30 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:5), gave 1.3 g (48%) of **35**: mp 215 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.08 (s, 3H), 6.34 (s, 1H), 6.74 (t, J = 9.0 Hz, 1H), 7.12 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 8.04 (d, J = 9.0 Hz, 2H), 8.10 (d, J = 9.0 Hz, 2H). HPLC purity (method 1): 99.9%. Anal. ($C_{19}H_{14}FBrO_5S$) C, H, S.

3-(4-Bromo-2-chlorophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (36) was prepared according to method I starting from **125** (2.18 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:5), gave 1.09 g (43%) of **36**: mp 214−215 °C; ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.08 (s, 3H), 6.37 (s, 1H), 6.58 (d, J = 8.5 Hz, 1H), 7.20 (d, J = 8.5 Hz, 1H), 7.56 (s, 1H), 8.03 (d, J = 7.5 Hz, 2H), 8.12 (d, J = 7.5 Hz, 2H). HPLC purity (method 1): 99.8%.

3-(4-Fluoro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (37) was prepared according to method I starting from **126** (11.15 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:3), gave 2.2 g (16%) of **37**: mp 146 °C; ^{1}H NMR (DMSO) δ 2.32 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 6.46 (s, 1H), 6.69−6.72 (m, 1H), 6.83−6.86 (m, 1H), 7.10−7.13 (m, 1H), 8.09 (s, 4H). HPLC purity (method 1): 96.7%.

3-(2-Chloro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (38) was prepared according to method I starting from **127** (10.01 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:1), gave 3.3 g (28%) of **38**: mp 159 °C; ^{1}H NMR (DMSO) δ 2.23 (s, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 6.48 (s, 1H), 6.81 (d, J = 8.7 Hz, 1H), 6.98 (d, J = 8.7 Hz, 1H), 7.32 (s, 1H), 8.07 (s, 4H). HPLC purity (method 1): 98.9%.

3-(4-Chloro-2-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (39) was prepared according to method I starting from **128** (6.4 g). Purification by flash chromatography, eluting with hexane/EtOAc (1:3), gave 1.14 g (15%) of **39**: mp 198 °C; ^{1}H NMR (DMSO) δ 2.31 (s, 3H), 2.44 (s, 3H), 3.27 (s, 3H), 6.47 (s, 1H), 6.72 (d, J = 9.0 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 7.32 (s, 1H), 8.08 (s, 4H). HPLC purity (method 1): 97.6%.

3-(2-Chloro-4-methoxyphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (40) was prepared according to method I starting from **129** (2.0 g). Purification by flash chromatography, eluting with hexane/EtOAc (3:7), gave 0.18 g (8%) of **40**: mp 171−172 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.08 (s, 3H), 3.74 (s, 3H), 6.34 (s, 1H), 6.64 (s, 2H), 6.97 (s, 1H), 8.02 (d, J = 8.7 Hz, 2H), 8.16 (d, J = 8.7 Hz, 2H). HPLC purity (method 1): 98.2%.

5.5. Synthesis of Pyrones 41−47. 3-Phenoxy-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (41). A mixture of 0.2 g (0.45 mmol) of compound **24**, 0.5 g (6.7 mmol) of sodium formate, 26 mg (0.02 mmol) of tetrakis(triphenylphosphine)-palladium(0), and 2 mL of DMF was heated at 100 °C for 16 h. Then the mixture was poured into water and extracted with EtOAc. The organic solution was dried, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography, eluting with hexane/EtOAc (1:1), to give 0.05 g (30%) of pure **41**: mp 169 °C; ^{1}H NMR (DMSO) δ 2.44 (s, 3H), 3.25 (s, 3H), 6.47 (s, 1H) 6.95−7.04 (m, 2H), 7.29 (m, 1H), 8.07 (m, 4H). HPLC purity (method 1): 98.3%. Anal. ($C_{19}H_{16}O_5S$) C, H, S.

General Procedure for the Synthesis of Pyrones 42−45. Method J. 2-(4-Methanesulfonylphenyl)-6-methyl-3-(2-methylphenoxy)pyran-4-one (42). To a solution of 1.4 g (0.032 mol) of **22** in 15 mL of DMF was added 43 mg (0.19 mmol) of palladium acetate, 0.23 g (0.77 mmol) of tri-*o*-tolylphosphine, 2.4 mL (0.017 mol) of tetramethyltin, and 1.45 mL (0.10 mol) of triethylamine. The mixture was heated to 100 °C during 4 days. After cooling, the reaction mixture was filtered through Celite and water was added to the filtrate. The aqueous phase was extracted with EtOAc, and the organic layer was washed with brine, dried, and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with hexane/EtOAc (1:2), to give 0.77 g (65%) of compound **42**: mp 168 °C; ^{1}H NMR (DMSO) δ 2.32 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.65 (d, J = 7.5 Hz, 1H), 6.92 (m, 1H), 7.02 (m, 1H), 7.22 (d, J = 7.2 Hz, 1H), 8.06 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 9.0 Hz, 2H). HPLC purity (method 1): 98.2%.

2-(4-Methanesulfonylphenyl)-6-methyl-3-(3-methylphenoxy)pyran-4-one (43) was prepared according to method J starting from **23** (1.15 g). Recrystallization from EtOH/water (1:2) gave 0.28 g (29%) of **43**: mp 162 °C; ^{1}H NMR (DMSO) δ 2.25 (s, 3H), 2.44 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.73−6.85 (m, 3H), 7.13−7.19 (m, 1H), 8.07 (s, 4H). HPLC purity (method 1): 95.0%.

2-(4-Methanesulfonylphenyl)-3-(4-methylphenoxy)-6-methylpyran-4-one (44) was prepared according to method J starting from **24** (0.16 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:3), gave 0.052 g (47%) of **44**: mp 185 °C; ^{1}H NMR (DMSO) δ 2.22 (s, 3H), 2.43 (s, 3H), 3.26 (s, 3H), 6.46 (s, 1H), 6.85 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 8.06 (m, 4H). HPLC purity (method 1): 98.5%. Anal. ($C_{20}H_{18}O_5S$) C, H, S.

3-(2-Fluoro-4-methylphenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (45) was prepared according to method J starting from **35** (0.83 g). Purification by flash chromatography, eluting with hexane/EtOAc (2:3), gave 0.45 g (64%) of **45**: mp 171 °C; ^{1}H NMR (DMSO) δ 2.24 (s, 3H), 2.43 (s, 3H), 3.27 (s, 3H), 6.47 (s, 1H), 6.83−6.90 (m, 2H), 7.12 (d, J = 12.0 Hz, 1H), 8.08 (s, 4H). HPLC purity (method 1): 99.6%.

3-(4-Aminophenoxy)-2-(4-methanesulfonylphenyl)-6-methylpyran-4-one (46). To a solution of 0.5 g (1.25 mmol) of compound **29** in 2 mL of EtOH/water (1:1) was added 0.21 g (3.7 mmol) of iron, and the mixture was heated to reflux for 20 min. After the mixture was cooled, 0.22 mL of HCl(conc) dissolved in 2 mL of EtOH/water (1:1) was added slowly and

the resulting mixture was refluxed for 2 h. After the mixture was cooled, active charcoal and more EtOH/water (1:1) were added with stirring and the mixture was filtered through Celite. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography, eluting with CH_2Cl_2/MeOH (93:7), to give 0.16 g (35%) of compound **46**: mp 212−213 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.07 (s, 3H), 6.34 (s, 1H), 6.60 (d, J = 8.7 Hz, 2H), 6.77 (d, J = 8.7 Hz, 2H), 7.99 (d, J = 8.4 Hz, 2H), 8.10 (d, J = 8.4 Hz, 2H). HPLC purity (method 1): 95.3%.

4-[2-(4-Methanesulfonylphenyl)-6-methyl-4-oxo-4*H*-pyran-3-yloxy]benzoic Acid (47). To a solution of 0.1 g (0.24 mmol) of compound **30** in 3 mL of dioxane were added 2.5 mL of water and 2.5 mL of HCl(conc). The mixture was heated to reflux for 5 h. After the mixture was cooled, water was added and the aqueous phase was extracted with EtOAc. The organic layer was washed with water and brine, dried, and concentrated to give a residue that was recrystallized from diethyl ether affording 0.082 g (85%) of compound **47**: mp 268−269 °C; ^{1}H NMR (DMSO) δ 2.45 (s, 3H), 3.26 (s, 3H), 6.51 (s, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.88 (d, J = 8.7 Hz, 2H), 8.06 (s, 4H), 12.80 (bs, 1H). HPLC purity (method 1): 99.4%.

Supporting Information Available: Elemental analysis data for the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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