Synthesis and Biological Evaluation of 3,4-Diaryloxazolones: A New Class of Orally Active Cyclooxygenase-2 Inhibitors

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A series of 3,4-diaryloxazolones 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. The replacement of the methyl sulfone group on the 4-phenyl ring by a sulfonamide moiety resulted in compounds with superior in vivo antiinflammatory properties. In the sulfonamide series, the introduction of a methyl group at the 5-position of the oxazolone ring gave rise to very COX-2-selective compounds but with decreased in vivo activity. Selected 3,4-diaryloxazolones exhibited excellent activities in experimental models of arthritis and hyperalgesia. The in vivo activity of these compounds was confirmed with the evaluation of their antipyretic effectiveness and their ability to inhibit migration of proinflammatory cells. As expected from their COX-2 selectivity, most of the active compounds lacked gastrointestinal toxicity in vivo in rats after a 4-day treatment of 100 mg/kg/day. Within this novel series, sulfonamides **9**−**11** have been selected for further preclinical evaluation.

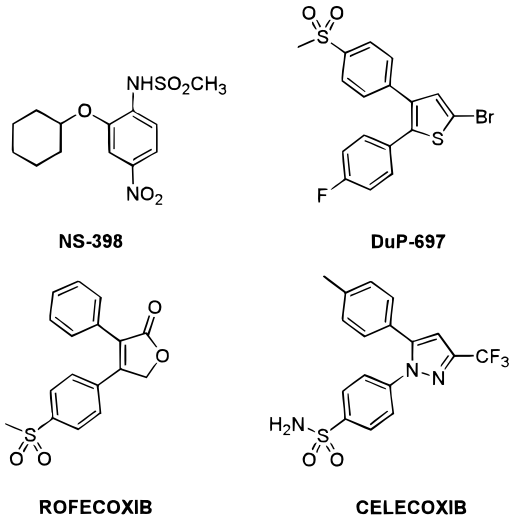
Introduction

The use of nonsteroidal antiinflammatory drugs (NSAIDs) for the treatment of inflammation and pain is often accompanied by gastrointestinal ulcerations and bleeding. The inhibition of cyclooxygenase (COX), the enzyme that catalyzes the conversion of arachidonic acid into prostaglandins and thromboxane, was considered for a long time to be responsible for both the therapeutic and the adverse effects of NSAIDs. In 1990, the existence of a second COX enzyme, named COX-2, was described.[1,2] COX-2 is an immediate-early gene induced by mitogenic and proinflammatory stimuli,[3] and it has been postulated to be the isoform involved in inflammatory processes.[4] In contrast, COX-1 is expressed constitutively and is believed to play a role in physiological processes such as gastroprotection and vascular homeostasis.[5] Currently available NSAIDs inhibit both COX-1 and COX-2, most of them exhibiting a selectivity for COX-1.[6]

The discovery and characterization of COX-2 suggested that selective inhibition of this enzyme might avoid the side effects of currently available NSAIDs while retaining their therapeutic efficacy. The hypothesis was partially proven when the first selective compounds, NS-398 and DuP-697 (Chart 1), were tested in animal models. Both compounds showed antiinflammatory, analgesic, and antipyretic activities, but they did not cause gastrointestinal lesions at high doses.[7−10]

Extensive libraries of selective COX-2 inhibitors have been developed by different laboratories in the last 5 years. Most of the compounds fit into three main categories: (1) acidic sulfonamides such as NS-398,[7] L-745,337,[11] and flosulide,[12] (2) diaryl heterocycles such as DuP-697,[9] rofecoxib,[13] and celecoxib[14] (Chart 1), and (3) modifications of classical NSAIDs such as zomepirac and indomethacin derivatives.

Chart 1. Structures of Some Selective COX-2 Inhibitors



Recently two selective COX-2 inhibitors, celecoxib and rofecoxib, have demonstrated efficacy in clinical trials of acute pain, osteoarthritis, and rheumatoid arthritis.[15−17] Furthermore, both compounds showed a superior gastrointestinal safety profile when compared to naproxen, diclofenac, or ibuprofen, confirming that this approach constitutes a promising alternative for the treatment of rheumatic diseases.

In this work we report the characterization of a new diaryl heterocyclic series, the 3,4-diaryloxazolones, a family of orally active, potent, and selective COX-2 inhibitors.

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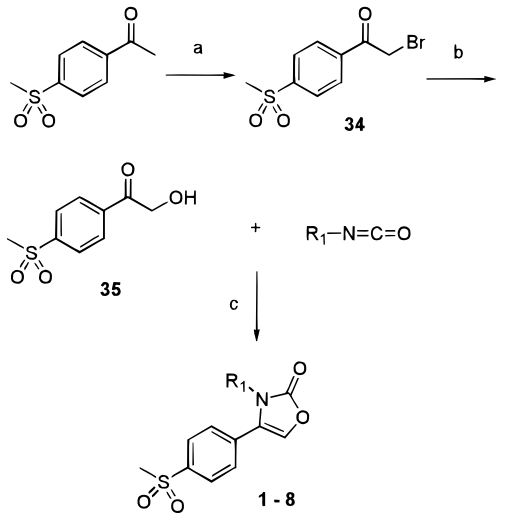
Scheme 1[a]



[a] Reagents: (a) Br_2, $CHCl_3$; (b) betaine, EtOH then saturated $NaHCO_3$; (c) 100 °C then AcOH, reflux.

Chemistry

The synthetic route for the sulfones **1**−**8** is outlined in Scheme 1. The commercially available 1-(4-methanesulfonylphenyl)ethanone was converted to the phenacyl alcohol **35** through the bromo derivative **34**. Thus, treatment of **34** with betaine yielded the intermediate ester which was hydrolyzed in situ to **35** in mild aqueous basic conditions. The addition of **35** to the appropriately substituted phenyl isocyanate and subsequent cyclization in acidic medium afforded the oxazolones **1**−**8** in moderate yields (21−56%).

In a similar way, the synthesis of the 5*H*-oxazolone (5HO) sulfonamide derivatives **9**−**28** (see Scheme 2) was achieved by the same addition/cyclization process starting from the phenacyl alcohol **38**. This intermediate alcohol was obtained from the commercially available sodium 4-acetylbenzenesulfonate in three steps comprising the formation of the sulfonamide **36**, its bromination to **37**, and final hydrolysis analogous to that described for the sulfone **35**. As mentioned above, the addition of **38** to the corresponding isocyanate and subsequent cyclization in acetic acid yielded the oxazolones **39**−**58**. Final debenzylation was achieved with concentrated sulfuric acid to give the target sulfonamides **9**−**28** (yields: 20−80%).

The 5-methyloxazolone (5MO) sulfonamide derivatives **29**−**33** were obtained from the corresponding 5HO sulfonamides via bromination and subsequent Stille coupling reaction with tetramethyltin (see Scheme 3), followed by debenzylation as described above for the 5HO analogues.

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.[18] This assay, in our hands, was much more predictive of functional selectivity and hence gastrointestinal safety than cell culture models such as monocytes or endothelial cells. Furthermore, the same whole blood assay has been used to evaluate the inhibition of COX-2 ex vivo after oral administration to healthy subjects.[19]

Potent and selective COX-2 inhibitors were evaluated in vivo in the rat carrageenan-induced foot paw edema model. Compounds showing good oral antiinflammatory activity in this model were then tested in an assay of inflammatory pain (hyperalgesia), in a chronic model of inflammation (adjuvant-induced arthritis), in an experimental model of fever (pyresis), and in a model of cellular infiltration (air pouch). Finally, gastrointestinal toxicity of selected compounds was evaluated in a 4-day administration protocol.

Results and Discussion

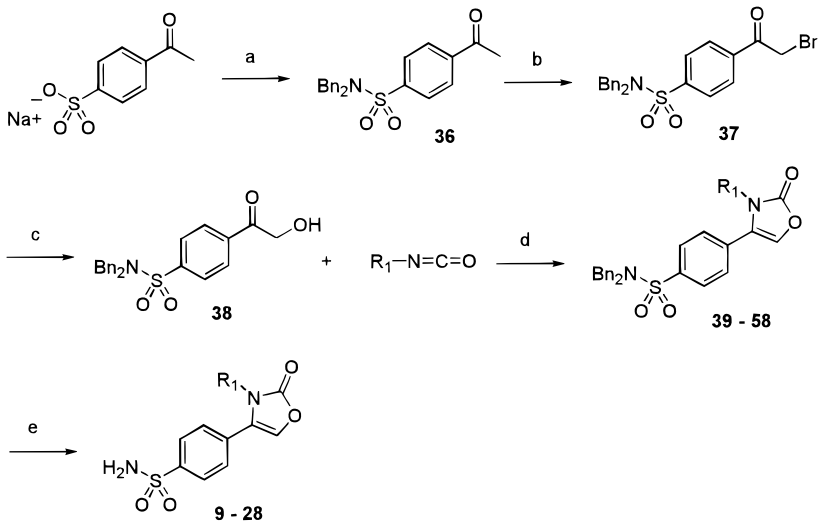
Structure−Activity Relationship. In the diaryl heterocyclic class of COX-2 inhibitors, it has been well-established that a *p*-methyl sulfone or sulfonamide on one of the phenyl groups is a requirement for good COX-2 potency and selectivity.[14,20] In the 3,4-diaryloxazolone series, we found that only the compounds with these substituents on the 4-phenyl ring were active. So, taking into account this structural restriction, we planned the structure−activity relationship work using 4-(4-methanesulfonylphenyl)oxazolone and 4-(4-sulfamoylphenyl)oxazolone as templates. Since the N3 substituents offered the most flexibility with regards to maintenance of COX-2 inhibitory activity, we explored modifications at this site while holding constant the 5-substituent as either hydrogen or methyl. Results are shown in Table 1.

In the 5HO sulfone family (compounds **1**−**8**), the presence of halogen atoms on the N3-phenyl ring generally enhanced the COX-2 activity with respect to the unsubstituted analogue **1**. The 2- and 4-fluoro derivatives (compounds **2** and **3**, respectively) were 3-fold more potent than compound **1**, while compound **8** (2,4-difluoro), with similar COX-2 activity, was less selective. The most active halogen derivative was **4** (4-chloro), with a potency similar to that of indomethacin and almost 50-fold selectivity. Increased COX-2 activity was maintained in the 4-alkyl analogues **6** and **7** with the latter compound being among the most selective. For the 4-trifluoromethyl derivative **5**, COX-2 potency was maintained while COX-1 was completely eliminated.

Preliminary results had shown that 5HO sulfones were less active in vivo after oral administration than the corresponding 5HO sulfonamides. This finding is in close agreement with literature results for related series.[14,21] Consequently, synthetic efforts were focused on the sulfonamide series.

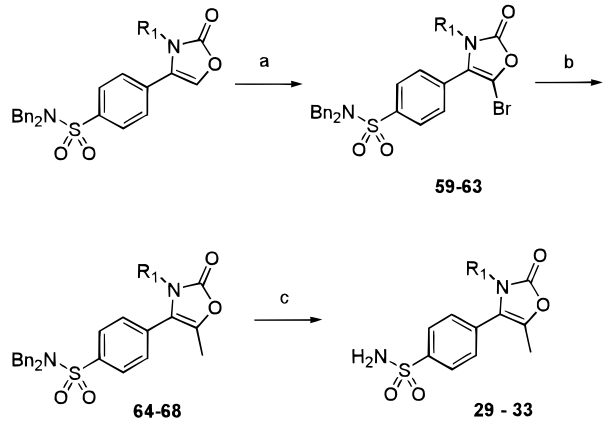
Within the 5HO sulfonamide analogues (compounds **9**−**28**), modifications at the N3 position also yielded interesting compounds. In general, introduction of substituents at the 3- and 4-positions of the N3-phenyl group resulted in more potent COX-2 inhibitors than the unsubstituted analogue **9**. By way of contrast, modifications at the 2-position gave more variable results. When the substituent was fluorine, the resulting compounds, **10** and **23**, were as potent as compound **9**, while the slightly more bulky substituents chlorine (compound **12**) and methyl (compound **16**) led to a reduction of activity. These results suggest that the steric effect of these substituents at the ortho position promotes a conformation with lower affinity for the

Scheme 2[a]



[a] Reagents: (a) $POCl_3$ then Bn_2NH, Et_3N, THF; (b) Br_2, $CHCl_3$; (c) betaine, EtOH then saturated $NaHCO_3$; (d) toluene, reflux then AcOH, reflux; (e) H_2SO_4.

Scheme 3[a]



[a] Reagents: (a) Br_2, $CHCl_3$; (b) Me_4Sn, $Pd(OAc)_2$, P(*o*-tolyl)$_3$, Et_3N, DMF; (c) H_2SO_4.

COX-2 enzyme. In the 3- and 4-methyl derivatives **17** and **18**, the COX-2 inhibitory activity and selectivity were enhanced with respect to their corresponding halogen-susbstituted analogues (compounds **11**, **13,** and **14**). As with the sulfone series, the introduction of 4-trifluoromethyl resulted in a complete loss of COX-1 activity, while the COX-2 potency was maintained. 4-Methoxy substitution (compound **20**) increased the affinity for both enzymes while reducing selectivity. The undesired COX-1 activity was modulated slightly by introduction of a halogen atom α to the 4-methoxy group (compounds **25** and **26**), in agreement with published literature.[14,21] By way of contrast, the same modification using the 4-chloro analogue **14** as a template gave a 3-fold improvement in COX-2 potency and a decrease in selectivity (compound **24**). The compounds substituted by a carboxylic group were completely inactive (compounds **21** and **22**). The non-phenyl derivatives cyclohexyl and 2-naphthyl (compounds **27** and **28**, respectively) were less potent.

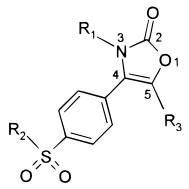
The COX-2 selectivity was significantly enhanced by the introduction of a methyl group at the 5-position of the oxazolone ring (5MO sulfonamides **29**−**33**), while the potency was maintained. For example, compound **33** showed a COX-2 activity comparable to its corresponding demethylated analogue **24** but was 5-fold more selective.

In summary, within the 3,4-diaryloxazolone series, we found COX-2 inhibitors as potent as indomethacin and with selectivities comparable to or greater than that of celecoxib.

In Vivo Activity. Compounds displaying reasonable COX-2 inhibitory activity and some degree of selectivity over COX-1 were evaluated by oral route in the carrageenan paw edema assay (Table 1). In the sulfone series, only the fluoro analogues **2**, **3,** and **8** showed a good inhibition of edema. Other derivatives (compounds **1** and **4**−**7**), despite good COX-2 potency, were moderately active in vivo. A lack of dose−response effect was observed for some of these compounds, with a plateau of an average of 30% inhibition at 3−30 mg/kg. No conclusive explanation for this behavior has been found. For the 5HO sulfonamide family, the activity in the carrageenan edema test was consistently good. Two of the most active compounds in this in vivo assay, the methylated analogues **17** and **18**, showed also the best COX-2 potency. The introduction of a 5-methyl substituent in the oxazolone ring caused a loss in oral activity. In general, ED_{35} values for 5MO sulfonamides were lower than those for their corresponding 5HO analogues.

A selected group of 3,4-diaryloxazolones with good activity in the carrageenan assay and/or superior COX-2 selectivity was evaluated by oral route in adjuvant-induced arthritis and carrageenan-induced hyperalgesia (Table 2). Superior in vivo activity was observed for the 5HO sulfonamide series. These compounds, when compared to their corresponding 5HO sulfone derivatives, displayed a 4−10-fold decrease in ED_{50} values in arthritis (see compounds **10** and **11** versus compounds **2** and **3**). Among the 5MO sulfonamides tested (compounds **29**, **30,** and **33**), compound **33** exhibited the best analgesic and antiarthritic profile. Furthermore, a decrease in ED_{50} values in both assays was observed for compounds **29** and **30** with respect to their corresponding 5HO sulfonamides.

Table 1. 4-Phenyloxazolones as COX Inhibitors



oxazolone series	compd	R_1	R_2	R_3	COX-1[a]	COX-2[a]	COX-1/COX-2	rat carrageenan paw edema[b]
5HO sulfone	**1**	C_6H_5	CH_3	H	33.6 ± 0.8	1.6 ± 0.3	21	24 ± 7
	2	2-FC_6H_4	CH_3	H	13.4 ± 3.2	0.66 ± 0.04	20	2.4
	3	4-FC_6H_4	CH_3	H	5.1 ± 1.3	0.51 ± 0.14	10	0.6
	4	4-ClC_6H_4	CH_3	H	13.6 ± 2.2	0.32 ± 0.05	42	10
	5	4-$CF_3C_6H_4$	CH_3	H	>100	2.0 ± 0.1	>50	21 ± 5
	6	4-$CH_3C_6H_4$	CH_3	H	11.6 ± 1.7	0.48 ± 0.01	24	27 ± 6
	7	4-$CH_3CH_2C_6H_4$	CH_3	H	42.4 ± 10.5	0.69 ± 0.24	61	23 ± 8
	8	2,4-diFC_6H_3	CH_3	H	6.94 ± 0.04	1.35 ± 0.06	5	1.4
5HO sulfonamide	**9**	C_6H_5	NH_2	H	24.4 ± 1.8	2.4 ± 0.7	10	0.4
	10	2-FC_6H_4	NH_2	H	27.9 ± 0.7	2.2 ± 0.9	13	1.7
	11	4-FC_6H_4	NH_2	H	13.2 ± 1.8	1.5 ± 0.4	9	2.0
	12	2-ClC_6H_4	NH_2	H	35.4 ± 8.2	6.5 ± 2.3	5	nt
	13	3-ClC_6H_4	NH_2	H	10.8 ± 4.6	1.5 ± 0.2	7	1.3
	14	4-ClC_6H_4	NH_2	H	7.0 ± 1.2	1.2 ± 0.2	6	1.6
	15	4-$CF_3C_6H_4$	NH_2	H	>100	2.0 ± 0.1	>50	2.4
	16	2-$CH_3C_6H_4$	NH_2	H	29.0 ± 1.4	9.7 ± 4.3	3	nt
	17	3-$CH_3C_6H_4$	NH_2	H	6.6 ± 1.0	0.51 ± 0.26	13	0.9
	18	4-$CH_3C_6H_4$	NH_2	H	10.9 ± 2.2	0.79 ± 0.04	14	0.7
	19	4-$CH_3CH_2C_6H_4$	NH_2	H	10.4 ± 4.7	1.56 ± 0.06	7	3.9
	20	4-$CH_3OC_6H_4$	NH_2	H	0.9 ± 0.2	0.21 ± 0.04	4	nt
	21	3-$HOOCC_6H_4$	NH_2	H	>100	>100	–	nt
	22	4-$HOOCC_6H_4$	NH_2	H	>100	59% ± 17	–	nt
	23	2,4-diFC_6H_3	NH_2	H	15.3 ± 1.0	2.3 ± 0.9	7	2.3
	24	3,4-diClC_6H_3	NH_2	H	1.5 ± 0.4	0.4 ± 0.1	4	nt
	25	4-CH_3O,3-FC_6H_3	NH_2	H	5.1 ± 2.2	1.13 ± 0.05	5	3.0
	26	4-CH_3O,3-ClC_6H_3	NH_2	H	5.8 ± 0.7	0.78 ± 0.14	7	2.4
	27	cyclohexyl	NH_2	H	>100	18.9 ± 5.0	>5	nt
	28	1-naphthyl	NH_2	H	37.1 ± 9.4	4.7 ± 2.1	8	13 ± 11
5MO sulfonamide	**29**	C_6H_5	NH_2	CH_3	49.3 ± 17.2	1.8 ± 0.5	27	1.7
	30	4-FC_6H_4	NH_2	CH_3	45.8 ± 14.0	0.51 ± 0.23	90	1.1
	31	3-$CH_3C_6H_4$	NH_2	CH_3	16.9 ± 3.5	0.93 ± 0.11	18	23 ± 7
	32	4-$CH_3C_6H_4$	NH_2	CH_3	43.5 ± 8.1	1.7 ± 0.2	26	2.6
	33	3,4-diClC_6H_3	NH_2	CH_3	8.7 ± 0.5	0.23 ± 0.05	38	4.4
	indomethacin				0.25 ± 0.03	0.22 ± 0.07	1	1.0
	naproxen				11.0 ± 1.4	18.9 ± 2.9	0.6	0.45
	celecoxib				14.2 ± 4.4	1.1 ± 0.2	13	1.1

[a] Data are indicated as IC_{50} (μM) or percentage of inhibition at 100 μM ± SEM ($n = 3$). [b] Data are indicated as ED_{35} (mg/kg) using four doses (6−8 animals/group) or percentage of inhibition at 3 mg/kg ± SEM (6−7 animals); nt: not tested.

The most active sulfonamides in arthritis ($ED_{50} < 2$ mg/kg) were further evaluated in pyresis and in the air pouch model (Table 2). Whereas all the compounds displayed good activity in the air pouch assay, compounds **15** and **33** showed a low potency as antipyretics. Both compounds were also the least active in arthritis.

The higher oral activity of the 5HO sulfonamide family, particularly in arthritis (a 7-day assay with once a day administration), suggests that these compounds might have a superior pharmacokinetic profile.

The evaluation of a selected group of sulfonamides on gastrointestinal toxicity (Table 3) showed that these compounds did not cause any ulceration or hemoglobin loss after a 4-day treatment at 100 mg/kg/day. Only compound **14** exhibited ulcerogenic properties, but these were very mild when compared to the classical NSAIDs indomethacin or naproxen. Another important indication of general toxicity, body weight loss, was not observed for any of the sulfonamides tested.

In conclusion, the overall pharmacological profiles of the 5HO sulfonamides tested were similar to or better than those exhibited by the reference compounds indomethacin, naproxen, and celecoxib. Excellent oral activity combined with a lack of gastrointestinal side effects suggests that these compounds could be a safer alternative to classical NSAIDs in the treatment of acute and chronic inflammatory processes.

Conclusions

We have identified a novel series of 3,4-diaryloxazolones as potent and selective COX-2 inhibitors. We have demonstrated that the replacement of the methyl sulfone group on the 4-phenyl ring by a sulfonamide moiety enhances in vivo potency. The in vitro COX-2 selectivity could be increased by the introduction of a methyl at the 5-position of the oxazolone ring, although there is a concomitant decrease in in vivo activity. A selected group of 3,4-diaryloxazolones exhibited excellent oral activity when tested in acute and chronic assays of inflammation, fever, and pain. Furthermore, these compounds were devoid of gastrointestinal toxicity at high doses. The overall pharmacological activity of the 3,4-diaryloxazolones suggests that these novel compounds constitute a promising series of oral antiinflam-

Table 2. In Vivo Pharmacological Profile of Selected Oxazolones

oxazolone series	compd	hyperalgesia[a]	adjuvant arthritis[a]	pyresis[a]	air pouch[b]
5HO sulfone	**2**	32	>3	nt	nt
	3	2.5	2.8	nt	nt
	8	21	2.5	nt	nt
5HO sulfonamide	**9**	1.1	0.15	0.5	1.2
	10	2.7	0.27	1.2	1.6
	11	3.9	0.6	2.4	0.4
	14	0.5	0.2	2.3	1.2
	15	8.1	1	11	2.6
	17	7.2	0.6	1.8	0.47
	18	3.8	0.34	3.3	1.7
5MO sulfonamide	**29**	7.7	>3	nt	nt
	30	14	3	nt	nt
	33	3	1.6	8.7	0.85
	indomethacin	1.2	0.22	1.5	2
	naproxen	5.2	6.1	0.8	1.4
	celecoxib	6.2	0.5	0.6	3

[a] Data are indicated as ED_{50} (mg/kg) using four doses, 6−8 animals/group. [b] Data are indicated as ED_{35} (mg/kg) using four doses, 6−8 animals/group; nt: not tested.

Table 3. Effect of Selected Oxazolones on Gastrointestinal Toxicity

oxazolone series	compd	dose (mg/kg)	PU[a]	NPU[a]	Hgb (g/dl)[b]
5HO sulfonamide	**9**	100	0	0	14.8
	10	100	0	0	11.6
	11	100	0	0	12.6
	14	100	3	2.1	12.5
	15	100	0	0	11.5
	17	100	0	0	12.8
	18	100	0	0	12.9
5MO sulfonamide	**33**	100	0	0	14.6
	indomethacin[c]	10	280	300	5.7*
	naproxen[c]	50	192	96	7.5*
	celecoxib	100	0	0	13.2

[a] PU: perforated ulcers; NPU: nonperforated ulcers. Results are expressed as ulcer score per incidence (percentage of animals with ulcers). [b] Hemoglobin levels for the vehicle-treated groups in the different assays ranged from 11.5 to 14.7 g/dl. [c] A significant body weight loss was only observed following indomethacin and naproxen treatments; *$p < 0.01$.

matory agents with the potential for an improved side effect profile. Compounds **9**−**11**, on the basis of their in vivo activity profiles and lack of gastrointestinal toxicity, have been selected for further preclinical and clinical profiling. Results of these studies will be reported in due course.

Experimental Section

COX-1 Activity in Human Whole Blood. Fresh blood from healthy volunteers who had not taken any NSAIDs for at least 7 days prior to blood extraction was collected in heparinized tubes (20 U/mL). Aliquots of 500 μL of blood were incubated either with 5 μL of vehicle (DMSO) or 5 μL of test compound solution for 1 h at 37 °C. Five to six different concentrations of each compound were used and determinations made in triplicate. Calcium ionophore A23187 (25 μM) was added 20 min before stopping the reaction. Plasma was separated by centrifugation (4 min at 13000 rpm) and kept at −30 °C until TXB_2 levels were measured using an ELISA kit (Amersham). IC_{50} values were obtained by nonlinear regression using InPlot, GraphPad software.

COX-2 Activity in Human Whole Blood. Aliquots of 500 μL of blood (obtained as indicated above) were incubated with either 5 μL of vehicle (DMSO) or 5 μL of test compound solution in the presence of LPS (10 μg/mL) for 24 h at 37 °C to induce COX-2 expression.[18] Five to six different concentrations of each compound were used and determinations made in triplicate. Plasma was separated by centrifugation (4 min at 13000 rpm) and kept at −30 °C until PGE_2 levels were measured using an ELISA kit (Amersham). IC_{50} values were obtained by nonlinear regression using InPlot, GraphPad software.

In Vivo Assays: General Procedures. Male Wistar rats (Interfauna, U.K., Ltd.) were used. Test compounds were suspended in a vehicle containing 0.5% methyl cellulose and 0.1% Tween and administered in a volume of 10 mL/kg. Unless indicated, rats were fasted with free access to water for 18 h prior to the assay. Statistical 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.

All the experimental protocols used in this paper have been approved by the appropriate animal ethics committees.

Carrageenan-Induced Plantar Edema in the Rat. The experimental protocol described by Winter et al. was used.[22] Rats (150−175 g) were randomly distributed in groups of 6 animals each, and at time 0, drug or vehicle was administered by oral route. One hour later, 0.1 mL of a carrageenan suspension (1% w/v in saline solution) was injected subcutaneously in the left hind paw of the animals. Volume of paw edema (mL) was measured using a water plethysmometer immediately after carrageenan injection and 3 h later. The increase in paw volume between time 0 and time +3 h was determined. The percentage of inhibition versus the mean value of the control group was calculated.

Carrageenan-Induced Hyperalgesia. Rats (200−230 g) were treated as previously described for the carrageenan edema test. Five hours after the injection of carrageenan, each animal was introduced in a transparent plastic cage (80 × 80 × 30 cm) with a wood shavings bed. The difficulty of walking was assessed by an observer unaware of the treatment. An score of 0, 1, or 2 was used indicating different degrees of disability in the movement of the inflammed paw. The score obtained by each animal was compared with that of the vehicle-treated group and the percentage of inhibition was calculated. Linear regression was used to calculate the ED_{50} values.

Adjuvant-Induced Arthritis. Rats (175−200 g) had free access to food and water along the assay. On day 0, the animals received an intraplantar injection of a suspension of *Mycobacterium tuberculosis* in paraffine oil (0.5 mg/rat) on the left hind paw. A group of 8 nonarthritic control rats were injected with paraffine oil alone. On days 11 and 14 after the induction of arthritis, the volume of the hind paws of each rat was measured using a water plethysmometer and rats whose paw volumes increased during that time were selected. Animals were distributed in groups of 8 animals having equivalent mean paw volumes and standard deviations.

Tests compounds were administered by oral route once daily for 7 days (days 14−20). Nonarthritic and arthritic control rats received vehicle alone for 7 days. Hind paw volumes were measured 20 h after the last dose (on day 21). Body weight was determined every day.

Percentages of inhibition of inflammation (measured as paw volume inhibition) and ED_{50} values were calculated for each treatment.

Pyresis. Rats (180−200 g) were randomly distributed in groups of 6 animals each. The day before drug administration, a measure of the body temperature was determined at 10:00 a.m. with a rectal probe (YSI, model LN-423) connected to a digital thermometer (Cibertec, model P-6). Six hours later, a suspension of 15% yeast extract (*Saccharomyces cerevisiae*) in saline (10 mg/kg) was injected subcutaneously at the back of the animals. A group of 6 animals received sterile saline alone (normothermic group). All animals were then fasted overnight with water ad libitum. The day after, a measure of rectal temperature was taken in the morning and 1 h later, the compounds were administered by oral route. A group of 6 animals injected with yeast extract (hyperthermic group) and the normothermic group received vehicle alone. Measurements

of rectal temperature were taken at intervals of 60 min for the next 5 h.

The area under the curve (AUC_{0-5h}) using the mean value of each treatment was calculated taking into account the maximum and minimum values stablished by both the hyperthermic and normothermic groups. The percentage of inhibition and the ED_{50} values were calculated for each treatment.

Ulcerogenic Activity. Rats (150−175 g) had free access to food and water along the assay. Animals were distributed at random in groups of 10 rats each. Vehicle or test compounds were administered by the oral route once a day for 4 consecutive days. In each experiment a group administered with 10 mg/kg indomethacin was included for interassay comparisons. Body weight was assessed every day. The animals were anesthetized 24 h after the last dosing, 1 mL of blood was extracted by cardiac puncture using heparin (10 U/mL) as anticoagulant, and the hemoglobin levels were measured. Rats were killed by cervical dislocation and the abdomen was incised along the midline. The whole intestine was removed, opened longitudinally, and gently washed. The macroscopic severity of the intestinal erosions was assessed using a parametric scale, evaluating the number of the perforated and nonperforated ulcers by means of a lesion index ranging from 0 to 3 (0: no ulcers, 1: <10 ulcers, 2: 10−25 ulcers, 3: >25 ulcers). The percentage of animals with both types of ulcers was also determined for each group. No gastric ulcers were observed using this protocol.

Carrageenan-Induced Air Pouch. Rats (150−175 g) were distributed at random in groups of 6 rats each. On day 0, animals received an injection of 20 mL of air into the subcutaneous tissue of the back. On day 3, vehicle or test compounds were administered by oral gavage. One hour later, 5 mL of a 0.4% carrageenan suspension was injected into the cavity. Five hours after carrageenan injection, rats were sacrificed, the air pouch was washed with 5 mL of saline and opened, and exudate volumes and number of white blood cells were recorded (Sismex K-800). Percentage of inhibition of the total cell number in the pouch and the ED_{50} values were determined for each treatment.

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.

2-Bromo-1-(4-methanesulfonylphenyl)ethanone (34). To a cooled solution of 5.40 g (27.3 mmol) of 1-(4-methanesulfonylphenyl)ethanone in 75 mL of $CHCl_3$ was added dropwise a solution of 1.23 mL (3.82 g, 24.0 mmol) of bromine in 10 mL of $CHCl_3$. After being stirred at −5 °C for 1 h, the mixture was warmed to room temperature and washed with water. The organic layer was dried and evaporated. The resulting solid was recrystallized from EtOAc /hexane (1:1) to give 5.80 g (77%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 8.15 (d, J = 8 Hz, 2H), 8.08 (d, J = 8 Hz, 2H), 4.46 (s, 2H), 3.10 (s, 3H).

2-Hydroxy-1-(4-methanesulfonylphenyl)ethanone (35). A mixture of 5.80 g (20.9 mmol) of **34** and 2.82 g (24.1 mmol) of betaine in 58 mL of EtOH was heated at 50 °C for 2 h. The reaction was cooled at 0 °C and the resulting solid was filtered and washed with isopropyl alcohol. The intermediate ester was dissolved in 100 mL of saturated $NaHCO_3$. After being stirred at room temperature for 15 min, the resulting solid was extracted with CH_2Cl_2. The organic layer was washed, dried, and concentrated to give 3.90 g (87%) of **35**: ^{1}H NMR ($CDCl_3$) δ 8.14 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 4.92 (s, 2H), 3.83 (br, 1H), 3.12 (s, 3H).

General Procedure for the Synthesis of Oxazolones 1−8. Method A. 4-(4-Methanesulfonylphenyl)-3-phenyl-3*H*-oxazol-2-one (1). A solution of 3.00 g (14.0 mmol) of **35** and 5 mL (5.48 g, 46.0 mmol) of phenyl isocyanate was heated at 100 °C for 2 h. After being cooled, the mixture was treated with ethyl ether. The resulting solid was filtered and suspended in 43 mL of acetic acid. The mixture was refluxed for 8 h, cooled, and diluted with 15 mL of EtOH. The crystallized solid was filtered and dried to yield 1.90 g (43%) of the title compound: mp 207−209 °C dec; ^{1}H NMR ($CDCl_3$) δ 7.83 (d, J = 8 Hz, 2H), 7.46−7.34 (m, 3H), 7.27 (d, J = 8 Hz, 2H), 7.23−7.14 (m, 3H), 3.00 (s, 3H). Anal. ($C_{16}H_{13}NO_4S$) C, H, N, S.

3-(2-Fluorophenyl)-4-(4-methanesulfonylphenyl)-3*H*-oxazol-2-one (2) was prepared according to method A starting from **35** (2.00 g) and 2-fluorophenyl isocyanate. Recrystallization from CH_3CN and ethyl ether gave 1.00 g (32%) of **2**: mp 186−187 °C; ^{1}H NMR (DMSO) δ 7.95 (s, 1H), 7.87 (d, J = 8 Hz, 2H), 7.61−7.50 (m, 2H), 7.42−7.31 (m, 2H), 7.38 (d, J = 8 Hz, 2H), 3.20 (s, 3H). Anal. ($C_{16}H_{12}FNO_4S$) C, H, N, S.

3-(4-Fluorophenyl)-4-(4-methanesulfonylphenyl)-3*H*-oxazol-2-one (3) was prepared according to method A starting from **35** (1.00 g) and 4-fluorophenyl isocyanate. Purification by flash chromatography, eluting with $CHCl_3$, gave 0.70 g (45%) of **3**: mp 167−168 °C; ^{1}H NMR (DMSO) δ 7.87 (d, J = 8 Hz, 2H), 7.84 (s, 1H), 7.41−7.28 (m, 4H), 7.34 (d, J = 8 Hz, 2H), 3.20 (s, 3H). Anal. ($C_{16}H_{12}FNO_4S$) C, H, N, S.

3-(4-Chlorophenyl)-4-(4-methanesulfonylphenyl)-3*H*-oxazol-2-one (4) was prepared according to method A starting from **35** (2.00 g) and 4-chlorophenyl isocyanate. Crystallization from EtOH/ethyl ether gave 1.80 g (55%) of **4**: mp 220 °C; ^{1}H NMR (DMSO) δ 8.00 (d, J = 8.5 Hz, 2H), 7.87 (s, 1H), 7.53 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.32 (d, J = 8.5 Hz, 2H), 3.23 (s, 3H). Anal. ($C_{16}H_{12}ClNO_4S$) C, H, N, S.

4-(4-Methanesulfonylphenyl)-3-(4-trifluoromethylphenyl)-3*H*-oxazol-2-one (5) was prepared according to method A starting from **35** (2.00 g) and 4-trifluoromethylphenyl isocyanate. Recrystallization from EtOH gave 2.00 g (56%) of **5**: mp 189−190 °C; ^{1}H NMR (DMSO) δ 7.92 (d, J = 8 Hz, 2H), 7.90 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H), 7.51 (d, J = 8 Hz, 2H), 7.38 (d, J = 8.5 Hz, 2H), 3.22 (s, 3H). Anal. ($C_{17}H_{12}F_3NO_4S$) C, H, N, S.

4-(4-Methanesulfonylphenyl)-3-(4-methylphenyl)-3*H*-oxazol-2-one (6) was prepared according to method A starting from **35** (2.00 g) and 4-methylphenyl isocyanate. Recrystallization from CH_3CN and isopropyl ether gave 0.80 g (26%) of **6**: mp 213-214 °C; ^{1}H NMR (DMSO) δ 7.87 (d, J = 8 Hz, 2H), 7.85 (s, 1H), 7.35 (d, J = 8 Hz, 2H), 7.27 (d, J = 8 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 3.21 (s, 3H), 2.31 (s, 3H). Anal. ($C_{17}H_{15}NO_4S$) C, H, N, S.

3-(4-Ethylphenyl)-4-(4-methanesulfonylphenyl)-3*H*-oxazol-2-one (7) was prepared according to method A starting from **35** (4.60 g) and 4-ethylphenyl isocyanate. Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.70 g (23%) of **7**: mp 199 °C; ^{1}H NMR (DMSO) δ 7.88 (s, 1H), 7.87 (d, J = 8 Hz, 2H), 7.36 (d, J = 8 Hz, 2H), 7.31 (d, J = 8 Hz, 2H), 7.21 (d, J = 8 Hz, 2H), 3.22 (s, 3H), 2.64 (q, J = 7.5 Hz, 2H), 1.19 (t, J = 7.5 Hz, 3H). Anal. ($C_{18}H_{17}NO_4S$) C, H, N, S.

3-(2,4-Difluorophenyl)-4-(4-methanesulfonylphenyl)-3*H*-oxazol-2-one (8) was prepared according to method A starting from **35** (2.00 g) and 2,4-difluorophenyl isocyanate. Purification by flash chromatography, eluting with EtOAc, gave 0.70 g (21%) of **8**: mp 155−156 °C; ^{1}H NMR (DMSO) δ 7.97 (s, 1H), 7.90 (d, J = 8.5 Hz, 2H), 7.70 (m, 1H), 7.52 (m, 1H), 7.38 (d, J = 8.5 Hz, 2H), 7.26 (m, 1H), 3.20 (s, 3H). Anal. ($C_{16}H_{11}F_2NO_4S$) C, H, N, S.

4-Acetyl-*N*,*N*-dibenzylbenzenesulfonamide (36). A mixture of 60.0 g (0.27 mol) of sodium 4-acetylbenzenesulfonate in 100 mL of $POCl_3$ was refluxed for 3 h. After being cooled, the solvent was evaporated, and the residue was partitioned between ethyl ether and water. The organic layer was washed, dried, and concentrated. The solid residue was dissolved in 200 mL of anhydrous THF, and the resulting solution was added dropwise to a mixture of 51.0 g (0.26 mol) of dibenzylamine and 36 mL (26.1 g, 0.26 mol) of triethylamine in 300 mL of anhydrous THF. After being stirred at room tempera-

ture overnight, the mixture was concentrated, and the residue was partitioned between EtOAc and water. The organic extracts were dried and concentrated. Crystallization from ethyl ether gave 73.7 g (72%) of the title compound: ^{1}H NMR (DMSO) δ 8.15 (d, J = 9 Hz, 2H), 8.00 (d, J = 9 Hz, 2H), 7.25−7.15 (m, 6H), 7.10 (m, 4H), 4.35 (s, 4H), 2.68 (s, 3H).

***N,N*-Dibenzyl-4-(2-bromoacetyl)benzenesulfonamide (37)**. To a solution of 73.7 g (0.19 mol) of **36** in 400 mL of $CHCl_3$ was added dropwise a solution of 9.9 mL (30.9 g, 0.19 mol) of bromine in 200 mL of $CHCl_3$. The mixture was stirred at room temperature for 1 h and concentrated. The resulting oil was dissolved in ethyl ether. After cooling, the obtained solid was filtered and recrystallized from EtOH to give 62.1 g (71%) of **37**: ^{1}H NMR ($CDCl_3$) δ 8.05 (d, J = 8 Hz, 2H), 7.90 (d, J = 8 Hz, 2H), 7.26−7.20 (m, 6H), 7.05 (m, 4H), 4.45 (s, 2H), 4.37 (s, 4H).

***N,N*-Dibenzyl-4-(2-hydroxyacetyl)benzenesulfonamide (38)**. A suspension of 41.8 g (0.091 mol) of **37** and 12.7 g (0.108 mol) of betaine in 250 mL of EtOH was heated at 60 °C for 5 h. The mixture was cooled and concentrated, and the residue was treated with EtOAc. The obtained solid was dissolved in 1 L of water. To the resulting solution was added dropwise 13 mL of saturated $NaHCO_3$. After being stirred 10 min, the solid was filtered, washed with water, and dried to give 27.4 g (76%) of **38**: ^{1}H NMR (DMSO) δ 8.10 (d, J = 8 Hz, 2H), 8.00 (d, J = 8 Hz, 2H), 7.30−7.15 (m, 6H), 7.06 (m, 4H), 5.30 (br, 1H), 4.86 (s, 2H), 4.30 (s, 4H).

General Procedure for the Synthesis of Oxazolones 39−58. Method B. *N,N*-Dibenzyl-4-(2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide (39). To a solution of 7.00 g (17.7 mmol) of **38** in 25 mL of toluene was added 2.10 mL (2.31 g, 19.4 mmol) of phenyl isocyanate. The mixture was refluxed for 2 h. After being cooled, the resulting solid was filtered and suspended in 70 mL of acetic acid. The mixture was refluxed for 8 h, cooled, and concentrated. The solid residue was crystallized with ethyl ether to yield 6.38 g (73%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.45−7.35 (m, 3H), 7.29−7.17 (m, 9H), 7.14 (d, J = 6 Hz, 2H), 7.03 (m, 4H), 4.36 (s, 4H).

***N,N*-Dibenzyl-4-[3-(2-fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (40)** was prepared according to method B starting from **38** (5.00 g) and 2-fluorophenyl isocyanate. Crystallization from ethyl ether gave 2.50 g (38%) of **40**: ^{1}H NMR (DMSO) δ 7.95 (s, 1H), 7.80 (d, J = 9 Hz, 2H), 7.66−7.51 (m, 2H), 7.46−7.35 (m, 2H), 7.32 (d, J = 9 Hz, 2H), 7.25−7.14 (m, 6H), 7.02 (m, 4H), 4.27 (s, 4H).

***N,N*-Dibenzyl-4-[3-(4-fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (41)** was prepared according to method B starting from **38** (8.00 g) and 4-fluorophenyl isocyanate. Crystallization from ethyl ether gave 6.15 g (59%) of **41**: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 9 Hz, 2H), 7.33−7.13 (m, 11H), 7.10 (d, J = 9 Hz, 2H), 7.03 (m, 4H), 4.32 (s, 4H).

***N,N*-Dibenzyl-4-[3-(2-chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (42)** was prepared according to method B starting from **38** (5.00 g) and 2-chlorophenyl isocyanate. Crystallization from isopropyl ether gave 2.29 g (34%) of **42**: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2H), 7.50 (m, 1H), 7.43−7.41 (m, 2H), 7.26−7.17 (m, 10H), 7.01 (m, 4H), 4.30 (s, 4H).

***N,N*-Dibenzyl-4-[3-(3-chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (43)** was prepared according to method B starting from **38** (5.00 g) and 3-chlorophenyl isocyanate. Crystallization from EtOH gave 2.30 g (34%) of **43**: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8 Hz, 2H), 7.39−7.14 (m, 13H), 7.04 (m, 4H), 4.33 (s, 4H).

***N,N*-Dibenzyl-4-[3-(4-chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (44)** was prepared according to method B starting from **38** (4.00 g) and 4-chlorophenyl isocyanate. Crystallization from EtOH gave 1.90 g (35%) of **44**: ^{1}H NMR ($CDCl_3$) δ 7.75 (d, J = 8.5 Hz, 2H), 7.46 (d, J = 8.5 Hz, 2H), 7.37 (d, J = 8.5 Hz, 2H), 7.29−7.12 (m, 9H), 7.05 (m, 4H), 4.33 (s, 4H).

***N,N*-Dibenzyl-4-[2-oxo-3-(4-trifluoromethylphenyl)-2,3-dihydrooxazol-4-yl]benzenesulfonamide (45)** was prepared according to method B starting from **38** (5.00 g) and 4-trifluoromethylphenyl isocyanate. Crystallization from ethyl ether gave 4.40 g (62%) of **45**: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 9 Hz, 2H), 7.64 (d, J = 9 Hz, 2H), 7.31 (d, J = 6 Hz, 2H), 7.27−7.18 (m, 7H), 7.14 (d, J = 6 Hz, 2H), 7.04 (m, 4H), 4.33 (s, 4H).

***N,N*-Dibenzyl-4-[3-(2-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (46)** was prepared according to method B starting from **38** (5.00 g) and 2-methylphenyl isocyanate. Crystallization from ethyl ether gave 2.96 g (46%) of **46**: ^{1}H NMR ($CDCl_3$) δ 7.65 (d, J = 9 Hz, 2H), 7.39−7.14 (m, 11H), 7.10 (d, J = 9 Hz, 2H), 7.02 (m, 4H), 4.31 (s, 4H), 2.22 (s, 3H).

***N,N*-Dibenzyl-4-[3-(3-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (47)** was prepared according to method B starting from **38** (10.0 g) and 3-methylphenyl isocyanate. Crystallization from ethyl ether gave 9.88 g (76%) of **47**: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 9 Hz, 2H), 7.31−7.10 (m, 12H), 7.02 (m, 4H), 6.89 (d, J = 7.5 Hz, 1H), 4.32 (s, 4H), 2.35 (s, 3H).

***N,N*-Dibenzyl-4-[3-(4-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (48)** was prepared according to method B starting from **38** (5.92 g) and 4-methylphenyl isocyanate. Crystallization from ethyl ether gave 2.66 g (35%) of **48**: ^{1}H NMR ($CDCl_3$) δ 7.70 (d, J = 9 Hz, 2H), 7.31−7.04 (m, 13H), 7.02 (m, 4H), 4.31 (s, 4H), 2.36 (s, 3H).

***N,N*-Dibenzyl-4-[3-(4-ethylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (49)** was prepared according to method B starting from **38** (3.00 g) and 4-ethylphenyl isocyanate. Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 0.50 g (13%) of **49**: ^{1}H NMR ($CDCl_3$) δ 7.72 (d, J = 8.7 Hz, 2H), 7.27−7.10 (m, 13H), 7.03 (m, 4H), 4.32 (s, 4H), 2.68 (q, J = 7.5 Hz, 2H), 1.24 (t, J = 7.5 Hz, 3H).

***N,N*-Dibenzyl-4-[3-(4-methoxyphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (50)** was prepared according to method B starting from **38** (12.0 g) and 4-methoxyphenyl isocyanate. Crystallization from ethyl ether gave 11.4 g (67%) of **50**: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8 Hz, 2H), 7.34−7.11 (m, 11H), 7.04 (m, 4H), 6.93 (d, J = 8 Hz, 2H), 4.34 (s, 4H), 3.80 (s, 3H).

3-[4-(4-Dibenzylsulfamoylphenyl)-2-oxo-2,3-dihydrooxazol-3-yl]benzoic Acid (51). To a solution of 4.00 g (10.1 mmol) of **38** in 20 mL of toluene was added 1.27 mL (1.93 g, 10.1 mmol) of 3-isocyanatobenzoic acid ethyl ester. The mixture was refluxed overnight. After being cooled, the resulting solid was filtered and suspended in 75 mL of acetic acid and 25 mL of 2 N HCl. The mixture was refluxed for 5 h, cooled, and concentrated. The residue was dissolved in CH_2Cl_2. The organic layer was washed with water, dried, and concentrated. The resulting oil was refluxed with 40 mL of acetic acid overnight. After being concentrated, the solid was crystallized with ethyl ether to yield 1.96 g (36%) of the title compound: ^{1}H NMR (DMSO) δ 8.10 (d, J = 8 Hz, 1H), 7.91 (s, 1H), 7.72 (d, J = 8 Hz, 2H), 7.54−7.38 (m, 3H), 7.28 (s, 1H), 7.24−7.18 (m, 7H), 7.03 (m, 4H), 4.31 (s, 4H).

4-[4-(4-Dibenzylsulfamoylphenyl)-2-oxo-2,3-dihydrooxazol-3-yl]benzoic acid (52) was obtained following the same procedure described for compound **51**, starting from 3.95 g (0.01 mmol) of **38** and 4-isocyanatobenzoic acid ethyl ester. Crystallization with ethyl ether gave 1.63 g (30%) of **52**: ^{1}H NMR (DMSO) δ 8.03 (d, J = 8 Hz, 2H), 7.92 (s, 1H), 7.82 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H), 7.30 (d, J = 8 Hz, 2H), 7.29−7.20 (m, 6H), 7.05 (m, 4H), 4.31 (s, 4H).

***N,N*-Dibenzyl-4-[3-(2,4-difluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (53)** was prepared according to method B starting from **38** (4.30 g) and 2,4-difluorophenyl isocyanate. Crystallization from EtOH gave 2.60 g (45%) of **53**: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2H), 7.39 (m, 1H), 7.31−7.18 (m, 8H), 7.14 (d, J = 9 Hz, 2H), 7.02 (m, 4H), 6.89 (m, 1H), 4.31 (s, 4H).

***N,N*-Dibenzyl-4-[3-(3,4-dichlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (54)** was prepared according to method B starting from **38** (5.00 g) and 3,4-dichlorophenyl isocyanate. Crystallization from EtOH gave

3.40 g (47%) of **54**: ^{1}H NMR (DMSO) δ 7.91 (s, 1H), 7.87 (d, J = 9 Hz, 2H), 7.78 (s, 1H), 7.75 (d, J = 9 Hz, 1H), 7.35 (d, J = 9 Hz, 2H), 7.29 (d, J = 9 Hz, 1H), 7.25−7.15 (m, 6H), 7.02 (m, 4H), 4.31 (s, 4H).

***N,N*-Dibenzyl-4-[3-(3-fluoro-4-methoxyphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (55).** To a solution of 5.31 g (37.6 mmol) of 3-fluoro-4-methoxyaniline in 100 mL of dry dioxane was added dropwise a solution of 2.3 mL (3.75 g, 18.8 mmol) of trichloromethyl chloroformate in 40 mL of dry dioxane. The mixture was heated at 60 °C overnight. After cooling, the solvent was concentrated and the residue was suspended in 200 mL of pentane. The insoluble material was filtered and washed with 3 × 50 mL of pentane, and the combined filtrates were concentrated. Crude 3-fluoro-4-methoxyphenyl isocyanate (3.50 g) was used, without further purification, in the preparation of **55**, which was prepared according to method B starting from **38** (7.44 g). Crystallization from ethyl ether gave 5.49 g (49%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 9 Hz, 2H), 7.30−7.16 (m, 9H), 7.41 (s, 1H), 7.06 (m, 4H), 6.97 (d, J = 9 Hz, 1H), 6.93 (s, 1H), 4.33 (s, 4H), 3.91 (s, 3H).

***N,N*-Dibenzyl-4-[3-(3-chloro-4-methoxyphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (56)** was prepared according to method B starting from **38** (5.00 g) and 3-chloro-4-methoxyphenyl isocyanate.[23] Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.50 g (21%) of **56**: ^{1}H NMR (DMSO) δ 7.87 (s, 1H), 7.82 (d, J = 8.7 Hz, 2H), 7.58 (s, 1H), 7.34 (d, J = 8.7 Hz, 2H), 7.26 (s, 1H), 7.22−7.19 (m, 7H), 7.04 (m, 4H), 4.28 (s, 4H), 3.89 (s, 3H).

***N,N*-Dibenzyl-4-(3-cyclohexyl-2-oxo-2,3-dihydrooxazol-4-yl)benzenesulfonamide (57)** was prepared according to method B starting from **38** (4.50 g) and cyclohexyl isocyanate. Crystallization from ethyl ether gave 1.50 g (26%) of **57**: ^{1}H NMR ($CDCl_3$) δ 7.89 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 7.27−7.22 (m, 6H), 7.10 (m, 4H), 6.83 (s, 1H), 4.36 (s, 4H), 3.49 (m, 1H), 2.31−2.19 (m, 2H), 1.86−1.62 (m, 5H), 1.26−1.16 (m, 3H).

***N,N*-Dibenzyl-4-[(3-naphthalen-1-yl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (58)** was prepared according to method B starting from **38** (7.00 g) and 1-naphthyl isocyanate. Crystallization from ethyl ether gave 7.36 g (76%) of **58**: ^{1}H NMR ($CDCl_3$) δ 8.03−7.91 (m, 2H), 7.77 (m, 1H), 7.62−7.27 (m, 9H), 7.24−7.06 (m, 6H), 7.00−6.89 (m, 4H), 4.20 (s, 4H).

General Procedure for the Synthesis of Oxazolones 59−63. Method C. *N,N*-Dibenzyl-4-(5-bromo-2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide (59). To a solution of 8.86 g (17.8 mmol) of **39** in 85 mL of $CHCl_3$ was added dropwise a solution of 0.95 mL (2.96 g, 18.5 mmol) of bromine in 10 mL of $CHCl_3$; meanwhile the evolved HBr was displaced by nitrogen. After being stirred at room temperature for 2 h, the mixture was washed with water and 40% $NaHSO_3$, dried, and concentrated. Crude **59** was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2H), 7.40−7.14 (m, 13H), 7.02 (m, 4H), 4.34 (s, 4H).

***N,N*-Dibenzyl-4-[5-bromo-3-(4-fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (60)** was prepared according to method C starting from **41** (7.41 g), to yield 7.60 g (89%) of **60**: ^{1}H NMR ($CDCl_3$) δ 7.77 (d, J = 9 Hz, 2H), 7.32−7.15 (m, 8H),7.13−6.95 (m, 8H), 4.35 (s, 4H).

***N,N*-Dibenzyl-4-[5-bromo-3-(3-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (61)** was prepared according to method C starting from **47** (3.00 g). Crude **61** was used in the next step without further purification: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 8.5 Hz, 2H), 7.30 (d, J = 8.5 Hz, 2H), 7.26−7.15 (m, 9H), 7.06−6.81 (m, 5H), 4.32 (s, 4H), 2.31 (s, 3H).

***N,N*-Dibenzyl-4-[5-bromo-3-(4-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (62)** was prepared according to method C starting from **48** (2.00 g). Crystallization from ethyl ether gave 1.60 g (69%) of **62**: ^{1}H NMR ($CDCl_3$) δ 7.74 (d, J = 9 Hz, 2H), 7.31 (d, J = 9 Hz, 2H), 7.27−7.21 (m, 8H), 7.17 (d, J = 9 Hz, 2H), 7.02 (m, 4H), 4.36 (s, 4H), 2.35 (s, 3H).

***N,N*-Dibenzyl-4-[5-bromo-3-(3,4-dichlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (63)** was prepared according to method C starting from **54** (5.54 g). Crystallization from ethyl ether gave 4.40 g (70%) of **63**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 9 Hz, 2H), 7.37 (s, 1H), 7.30 (d, J = 9 Hz, 2H), 7.27−7.14 (m, 7H), 7.09 (m, 4H), 6.88 (d, J = 9 Hz, 1H), 4.37 (s, 4H).

General Procedure for the Synthesis of Oxazolones 64−68. Method D. *N,N*-Dibenzyl-4-(5-methyl-2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide (64). To a solution of crude **59** (17.8 mmol) in 45 mL of anhydrous DMF were added 6.36 g (35.6 mmol) of tetramethyltin, 0.07 g (0.33 mmol) of palladium(II) acetate, 0.43 g (1.42 mmol) of tri-*o*-tolylphosphine, and 2.46 mL (1.79 g, 17.8 mmol) of Et_3N. The mixture was heated at 100 °C overnight. After being cooled, the mixture was diluted with 45 mL of dioxane and filtered through Celite. The filtrate was partitioned between EtOAc and water. The organic layer was washed, dried, and concentrated. The residue was purified by column chromatography, eluting with EtOAc/hexane (1:2), to give 6.46 g (71%) of the title compound: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2H), 7.35−7.07 (m, 13H), 7.02 (m, 4H), 4.33 (s, 4H), 2.31 (s, 3H).

***N,N*-Dibenzyl-4-[3-(4-fluorophenyl)-5-methyl-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (65)** was prepared according to method D starting from **60** (4.65 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 1.86 g (45%) of **65**: ^{1}H NMR ($CDCl_3$) δ 7.76 (d, J = 9 Hz, 2H), 7.31−7.10 (m, 10H), 7.17 (d, J = 9 Hz, 2H), 7.06 (m, 4H), 4.36 (s, 4H), 2.29 (s, 3H).

***N,N*-Dibenzyl-4-[5-methyl-3-(3-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (66)** was prepared according to method D starting from crude **60** (3.00 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 2.10 g (79%) of **66**: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 8 Hz, 2H), 7.24−7.20 (m, 7H), 7.17 (d, J = 8 Hz, 2H), 7.12−6.78 (m, 7H), 4.33 (s, 4H), 2.32 (s, 3H), 2.30 (s, 3H).

***N,N*-Dibenzyl-4-[5-methyl-3-(4-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (67)** was prepared according to method D starting from **62** (1.56 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 0.74 g (54%) of **67**: ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 9 Hz, 2H), 7.30−7.20 (m, 8H), 7.14 (d, J = 9 Hz, 2H), 7.09−6.93 (m, 6H), 4.33 (s, 4H), 2.35 (s, 3H), 2.30 (s, 3H).

***N,N*-Dibenzyl-4-[3-(3,4-dichlorophenyl)-5-methyl-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (68)** was prepared according to method D starting from **63** (5.55 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 3.37 g (75%) of **68**: ^{1}H NMR ($CDCl_3$) δ 7.80 (d, J = 9 Hz, 2H), 7.44−7.19 (m, 8H), 7.16 (d, J = 9 Hz, 2H), 7.06 (m, 4H), 6.87 (d, J = 6 Hz, 1H), 4.36 (s, 4H), 2.33 (s, 3H).

General Procedure for the Synthesis of Oxazolones 9−33. Method E. 4-(2-Oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide (9). A suspension of 6.38 g (12.8 mmol) of **39** in 17 mL of concentrated H_2SO_4 was stirred at room temperature for 20 min. The mixture was poured into ice. The resulting solid was filtered, washed with water, and dried. Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 2.81 g (69%) of the title compound: mp 208 °C; ^{1}H NMR (DMSO) δ 7.82 (s, 1H), 7.73 (d, J = 8.7 Hz, 2H), 7.50−7.42 (m, 3H), 7.40 (s, 2H), 7.31−7.26 (m, 2H), 7.29 (d, J = 8.7 Hz, 2H). Anal. ($C_{15}H_{12}N_2O_4S$) C, H, N, S.

4-[3-(2-Fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (10) was prepared according to method E starting from **40** (2.50 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 0.60 g (37%) of **10**: mp 176−178 °C; ^{1}H NMR (DMSO) δ 7.88 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.61−7.51 (m, 2H), 7.43 (m, 1H), 7.40 (s, 2H), 7.37 (m, 1H), 7.33 (d, J = 8.5 Hz, 2H). Anal. ($C_{15}H_{11}FN_2O_4S$) C, H, N, S.

4-[3-(4-Fluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (11) was prepared according to method E starting from **41** (4.90 g). Recrystallization from EtOH/CH_2Cl_2

gave 1.40 g (44%) of **11**: mp 211−213 °C; ^{1}H NMR (DMSO) δ 7.81 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.40 (s, 2H), 7.38−7.34 (m, 4H), 7.30 (d, J = 8.5 Hz, 2H). Anal. ($C_{15}H_{11}FN_2O_4S$) C, H, N, S.

4-[3-(2-Chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (12) was prepared according to method E starting from **42** (8.50 g). Recrystallization from EtOAc gave 1.97 g (30%) of **12**: mp 169 °C; ^{1}H NMR (DMSO) δ 7.90 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.71−7.63 (m, 2H), 7.55−7.50 (m, 2H), 7.39 (s, 2H), 7.29 (d, J = 8.5 Hz, 2H). Anal. ($C_{15}H_{11}ClN_2O_4S$) C, H, N, S.

4-[3-(3-Chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (13) was prepared according to method E starting from **43** (2.30 g). Purification by flash chromatography, eluting with CH_2Cl_2/MeOH (95:5), gave 0.80 g (53%) of **13**: mp 176−177 °C; ^{1}H NMR (DMSO) δ 7.83 (s, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.53 (m, 1H), 7.49 (m, 1H), 7.46 (s, 1H), 7.42 (s, 2H), 7.32 (d, J = 8.5 Hz, 2H), 7.19 (m, 1H). Anal. ($C_{15}H_{11}ClN_2O_4S$) C, H, N, S.

4-[3-(4-Chlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (14) was prepared according to method E starting from **44** (1.90 g). Recrystallization from CH_3CN gave 0.50 g (40%) of **14**: mp 213−214 °C; ^{1}H NMR (DMSO) δ 7.82 (s, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.41 (s, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.7 Hz, 2H). Anal. ($C_{15}H_{11}ClN_2O_4S$) C, H, N, S.

4-[2-Oxo-3-(4-trifluoromethylphenyl)-2,3-dihydrooxazol-4-yl]benzenesulfonamide (15) was prepared according to method E starting from **45** (4.40 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.65 g (55%) of **15**: mp 196 °C; ^{1}H NMR (DMSO) δ 7.84 (s, 1H), 7.83 (d, J = 8 Hz, 2H), 7.76 (d, J = 8 Hz, 2H), 7.48 (d, J = 8 Hz, 2H), 7.40 (s, 2H), 7.29 (d, J = 8 Hz, 2H). Anal. ($C_{16}H_{11}F_3N_2O_4S$) C, H, N, S.

4-[3-(2-Methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (16) was prepared according to method E starting from **46** (2.96 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 0.80 g (42%) of **16**: mp 99−101 °C; ^{1}H NMR (DMSO) δ 7.91(s, 1H), 7.70 (d, J = 8 Hz, 2H), 7.42−7.20 (m, 6H), 7.40 (s, 2H), 2.14 (s, 3H). Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N, S.

4-[3-(3-Methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (17) was prepared according to method E starting from **47** (16.0 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 7.26 g (70%) of **17**: mp 192 °C; ^{1}H NMR (DMSO) δ 7.82 (s, 1H), 7.74 (d, J = 8.7 Hz, 2H), 7.40 (s, 2H), 7.32 (m, 1H), 7.29 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8 Hz, 1H), 7.20 (s, 1H) 7.01 (d, J = 8 Hz, 1H), 2.31 (s, 3H). Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N, S.

4-[3-(4-Methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (18) was prepared according to method E starting from **48** (2.66 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 1.00 g (58%) of **18**: mp 223 °C; ^{1}H NMR (DMSO) δ 7.80 (s, 1H), 7.74 (d, J = 8 Hz, 2H), 7.40 (s, 2H), 7.29 (d, J = 8.7 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8 Hz, 2H), 2.33 (s, 3H). Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N, S.

4-[3-(4-Ethylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (19) was prepared according to method E starting from **49** (0.50 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 0.25 g (79%) of **19**: mp 199 °C; ^{1}H NMR (DMSO) δ 7.81 (s, 1H), 7.73 (d, J = 8 Hz, 2H), 7.39 (s, 2H), 7.30 (d, J = 8 Hz, 4H), 7.19 (d, J = 8 Hz, 2H), 2.64 (q, J = 7.5 Hz, 2H), 1.86 (t, J = 7.5 Hz, 3H). Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N, S.

4-[3-(4-Methoxyphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide (20) was prepared according to method E starting from **50** (11.40 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 1.40 g (20%) of **20**: mp 196 °C; ^{1}H NMR ($CDCl_3$) δ 7.84 (d, J = 8.7 Hz, 2H), 7.23 (d, J = 8.7 Hz, 2H), 7.13 (s, 1H), 7.12 (d, J = 9 Hz, 2H), 6.92 (d, J = 9 Hz, 2H), 4.78 (s, 2H), 3.82 (s, 3H). Anal. ($C_{16}H_{14}N_2O_5S$) H, N, S; C: calcd, 55.48; found, 56.01.

3-[2-Oxo-4-(4-sulfamoylphenyl)-2,3-dihydrooxazol-3-yl]-benzoic acid (21) was prepared according to method E starting from **51** (1.95 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc/MeOH (1:78:10:5), gave 0.83 g (66%) of **21**: mp 253 °C; ^{1}H NMR (DMSO) δ 12.87 (br, 1H), 7.97 (d, J = 8.5 Hz, 1H), 7.91 (s, 1H), 7.86 (s, 1H), 7.68 (d, J = 8.5 Hz, 2H), 7.57 (t, J = 8.5 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.40 (s, 2H), 7.31 (d, J = 8.5 Hz, 2H). Anal. ($C_{16}H_{12}N_2O_6S$) H, N, S; C: calcd, 53.33; found, 53.92.

4-[2-Oxo-4-(4-sulfamoylphenyl)-2,3-dihydrooxazol-3-yl]-benzoic acid (22) was prepared according to method E starting from **52** (1.63 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc/MeOH (1:78:10:5), gave 0.52 g (48%) of **22**: mp 236 °C; ^{1}H NMR (DMSO) δ 12.90 (br, 1H), 8.02 (d, J = 8.3 Hz, 2H), 7.86 (s, 1H), 7.78 (d, J = 8.3 Hz, 2H), 7.42, (s, 2H), 7.40 (d, J = 8.3 Hz, 2H), 7.31 (d, J = 8.3 Hz, 2H). Anal. ($C_{16}H_{12}N_2O_6S\cdot 0.2H_2O$) C, H, S; N: calcd, 7.70; found, 7.21.

4-[3-(2,4-Difluorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide (23) was prepared according to method E starting from **53** (2.60 g). Recrystallization from MeOH gave 0.50 g (30%) of **23**: mp 190−191 °C; ^{1}H NMR ($CDCl_3$) δ 7.85 (d, J = 8.5 Hz, 2H), 7.40 (m, 1H), 7.22 (s, 1H), 7.21 (d, J = 8.5 Hz, 2H), 7.04−6.93 (m, 2H), 6.71 (s, 2H). Anal. ($C_{15}H_{10}F_2N_2O_4S$) C, H, N, S.

4-[3-(3,4-Dichlorophenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (24) was prepared according to method E starting from **54** (3.40 g). Purification by flash chromatography, eluting with $CHCl_3$/MeOH (20:1), gave 1.49 g (64%) of **24**: mp 157−159 °C dec; ^{1}H NMR (DMSO) δ 7.83 (s, 1H), 7.80 (s, 1H), 7.74 (d, J = 8.5 Hz, 2H), 7.71 (d, J = 8.5 Hz, 2H), 7.41 (s, 2H), 7.31 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H). Anal. ($C_{15}H_{10}Cl_2N_2O_4S$) C, H, N, S.

4-[3-(3-Fluoro-4-methoxyphenyl)-2-oxo-2,3-dihydro-oxazol-4-yl]benzenesulfonamide (25) was prepared according to method E starting from **55** (9.78 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 3.60 g (55%) of **25**: mp 184 °C; ^{1}H NMR (DMSO) δ 7.80 (s, 1H), 7.77 (d, J = 8 Hz, 2H), 7.40−7.35 (m, 3H), 7.32 (d, J = 8 Hz, 2H), 7.23 (t, J = 9.5 Hz, 1H), 7.08 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H). Anal. ($C_{16}H_{13}FN_2O_5S$) C, H, N, S.

4-[3-(3-Chloro-4-methoxyphenyl)-2-oxo-2,3-dihydro-oxazol-4-yl]benzenesulfonamide (26) was prepared according to method E starting from **56** (1.50 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.68 g (67%) of **26**: mp 194 °C; ^{1}H NMR (DMSO) δ 7.80 (s, 1H), 7.76 (d, J = 8.7 Hz, 2H), 7.55 (m, 1H), 7.40 (s, 2H), 7.32 (d, J = 8.7 Hz, 2H), 7.22−7.20 (m, 2H), 3.88 (s, 3H). Anal. ($C_{16}H_{13}ClN_2O_5S$) C, H, N, S.

4-(3-Cyclohexyl-2-oxo-2,3-dihydrooxazol-4-yl)benzenesulfonamide (27) was prepared according to method E starting from **57** (1.50 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:1), gave 0.40 g (42%) of **27**: mp 167−169 °C; ^{1}H NMR (DMSO) δ 7.94 (d, J = 8.5 Hz, 2H), 7.61 (d, J = 8.5 Hz, 2H), 7.50 (s, 2H), 7.42 (s, 1H), 3.46 (m, 1H), 2.13−2.00 (m, 2H), 1.77−1.74 (m, 4H), 1.55 (m, 1H), 1.18−1.06 (m, 3H). Anal. ($C_{15}H_{18}N_2O_4S$) C, H, N, S.

4-[(3-Naphthalen-1-yl)-2-oxo-2,3-dihydrooxazol-4-yl]-benzenesulfonamide (28) was prepared according to method E starting from **58** (7.36 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 1.81 g (37%) of **28**: mp 186 °C; ^{1}H NMR (DMSO) δ 8.10−8.04 (m, 2H), 8.00 (s, 1H), 7.75 (m, 1H), 7.67−7.59 (m, 4H), 7.60 (d, J = 8 Hz, 2H), 7.28 (s, 2H), 7.24 (d, J = 8 Hz, 2H). Anal. ($C_{19}H_{14}N_2O_4S\cdot 0.35H_2O$) C, H, S; N: calcd, 7.52; found, 7.02.

4-(5-Methyl-2-oxo-3-phenyl-2,3-dihydrooxazol-4-yl)benzenesulfonamide (29) was prepared according to method E starting from **64** (6.46 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 2.90 g (70%) of **29**: mp 101 °C; ^{1}H NMR (DMSO) δ 7.73 (d, J = 6 Hz, 2H), 7.41−7.35 (m, 5H), 7.20 (d, J = 6 Hz, 2H), 7.18 (d, J = 7 Hz, 2H), 2.21 (s, 3H). Anal. ($C_{16}H_{14}N_2O_4S$) C, H, N, S.

4-[3-(4-Fluorophenyl)-5-methyl-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (30) was prepared according to

method E starting from **65** (2.96 g). Purification by flash chromatography, eluting with EtOAc/hexane (1:2), gave 1.20 g (61%) of **30**: mp 100−105 °C; ^{1}H NMR (DMSO) δ 7.77 (d, J = 8.5 Hz, 2H), 7.40 (s, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.29−7.25 (m, 4H), 2.22 (s, 3H). Anal. ($C_{16}H_{13}FN_2O_4S$) C, H, N, S.

4-[5-Methyl-3-(3-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (31) was prepared according to method E starting from **66** (1.60 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 0.83 g (80%) of **31**: mp 165 °C; ^{1}H NMR (DMSO) δ 7.75 (d, J = 8.5 Hz, 2H), 7.41 (s, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.25 (m, 1H), 7.17−7.12 (m, 2H), 6.90 (m, 1H), 2.27 (s, 3H), 2, 23 (s, 3H). Anal. ($C_{17}H_{16}N_2O_4S$) C, H, N, S.

4-[5-Methyl-3-(4-methylphenyl)-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (32) was prepared according to method E starting from **67** (0.74 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 0.37 g (76%) of **32**: mp 103−104 °C; ^{1}H NMR (DMSO) δ 7.77 (d, J = 8 Hz, 2H), 7.39 (s, 2H), 7.30 (d, J = 8 Hz, 2H), 7.18 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 8.5 Hz, 2H), 2.26 (s, 3H), 2.19 (s, 3H). Anal. ($C_{17}H_{16}N_2O_4S$) C, H, N, S.

4-[3-(3,4-Dichlorophenyl)-5-methyl-2-oxo-2,3-dihydrooxazol-4-yl]benzenesulfonamide (33) was prepared according to method E starting from **68** (3.37 g). Purification by flash chromatography, eluting with AcOH/CH_2Cl_2/EtOAc (1:78:10), gave 1.44 g (62%) of **33**: mp 132−135 °C; ^{1}H NMR (DMSO) δ 7.81 (d, J = 8 Hz, 2H), 7.66 (d, J = 7 Hz, 1H), 7.65 (s, 1H), 7.43 (s, 2H), 7.36 (d, J = 8 Hz, 2H), 7.11 (d, J = 7 Hz, 1H), 2.23 (s, 3H). Anal. ($C_{16}H_{12}Cl_2N_2O_4S$) C, H, N, S.

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