Design and Synthesis of Novel Rofecoxib Analogs as Potential Cyclooxygenase (COX-2) Inhibitors: Replacement of the Methylsulfonyl Pharmacophore by a Sulfonylazide Bioisostere

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A group of rofecoxib analogs, having a sulfonylazide (SO_2N_3) substituent in place of the methanesulfonyl (SO_2CH_3) pharmacophore at the *meta*-position *viz* 3-(4-methyl, 4-methoxy, or 4-ethoxyphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7a-c**) and *para*-position *viz* 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**), 3-(4-fluoro, or 4-chlorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e-f**) of the C-4 phenyl ring, and 4-(1-oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**) were designed and synthesized for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. *In vitro* COX-1/COX-2 enzyme inhibition studies showed that 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**) inhibited COX-1 selectively (COX-1 IC_{50} = 0.6659 μM; COX-2 IC_{50} > 100 μM) and 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**) inhibited both enzymes (COX-1 IC_{50} = 0.8494 μM; COX-2 IC_{50} = 1.7661 μM). A molecular modeling study was performed where 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**) was docked in the active site of murine COX-2 isozyme, which showed that the sulfonylazido group inserts deep into the 2º-pocket of COX-2 where it undergoes both *H*-bonding (Gln^{192}, Phe^{518}) and weak electrostatic (Arg^{513}) interactions.

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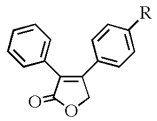
Introduction.

The discovery that the inducible cyclooxygenase-2 (COX-2) isozyme is involved in inflammatory processes, and that the constitutively expressed cyclooxygenase-1 (COX-1) isozyme plays a role in gastroprotection and vascular homeostasis, suggested that selective inhibition of COX-2 would circumvent the adverse ulcerogenic effect associated with classical non-steroidal antiinflammatory drugs (NSAIDs). This assumption provided the rationale for design of the non-ulcerogenic selective COX-2 inhibitors celecoxib [1] and rofecoxib [2]. The sulfonamide (SO_2NH_2) pharmacophore present in celecoxib, and the SO_2CH_3 pharmocophore present in rofecoxib, are believed to induce COX-2 selectivity by insertion into the secondary (2°) COX-2 pocket, which is absent in COX-1, with subsequent *H*-bonding of their oxygen and/or nitrogen atoms to arginine (Arg^{513}), or the amide hydrogen of phenylalanine (Phe^{518}). Replacement of histidine (His^{513}) in COX-1 by arginine (Arg^{513}) in COX-2 has been reported to play a key role in the hydrogen-bond network of the cyclooxygenase active site. Histidine (His^{90}), glutamine (Gln^{192}), and tyrosine (Tyr^{355}) control the access of ligands into the 2º COX-2 pocket [3]. The interaction of arginine (Arg^{513}) with the bound ligand has been reported to be a requirement for the time-dependent inhibition of COX-2 [4]. The presence of the arginine (Arg^{513}) residue in the 2º-pocket of COX-2 had not been exploited for the design of selective COX-2 inhibitors prior to our recent study involving replacement of the SO_2NH_2 (celecoxib) and SO_2CH_3 (rofecoxib) pharmacophores by a bioisosteric dipolar azido substituent. In this regard, a molecular modeling study, where the azido-rofecoxib (**2**) *viz* 4-(4-azidophenyl)-3-phenyl-2(5*H*)furanone was docked in the active site of the COX-2 isozyme, showed that the terminal nitrogen atom of the linear azido (N_3) group was inserted deep into the 2º-pocket of the COX-2 binding site, undergoing an electrostatic interaction with the guanidino group of Arg^{513} [5].



1, R = SO_2CH_3, Rofecoxib [2]**; 2**, R = N_3 [5]

Figure 1

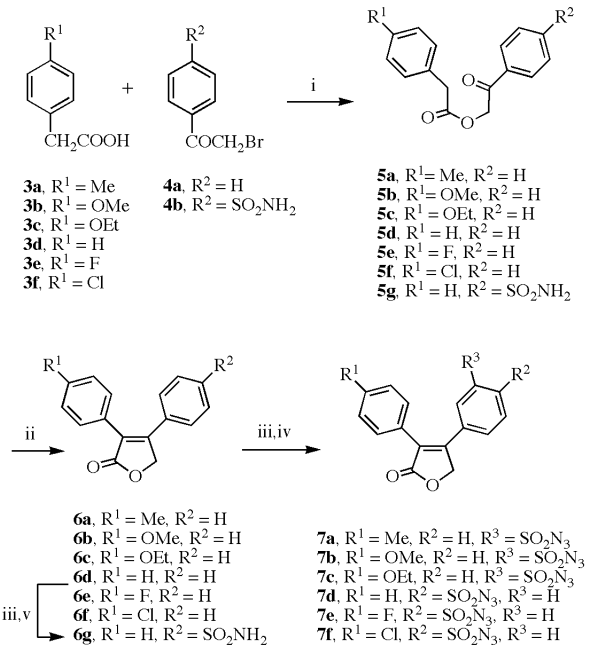
This study has now been extended to include a novel dipolar sulfonylazido (SO_2N_3) pharmacophore that has the potential to undergo dual *H*-bonding (sulfonyl oxygens) and electrostatic (ion-ion) interactions (N_3) with amino acid residues lining the 2º-pocket of the COX-2 binding site. Accordingly, we now describe the design, synthesis, cyclooxygenase (*in viro* COX-1/COX-2 enzyme inhibition assay) inhibitory activities, and some molecular modeling studies for a group of rofecoxib analogs having a SO_2N_3 moiety at the *meta*-position *viz* 3-(4-methyl, 4-methoxy, or 4-ethoxyphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7a-c**) and at the *para*-position *viz* 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**), 3-(4-fluoro, or 4-chlorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e-f**) of the C-4 phenyl ring, and 4-(1-oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**) .

Chemistry.

A group of 4-(3-sulfonylazidophenyl)- **7a-c**, and 4-(4-sulfonylazidophenyl)- **7d-f** derivatives of 3-phenyl-

2(5*H*)furanone were synthesized using the reaction sequence illustrated in Scheme 1. Accordingly, condensation [5] of a phenylacetic acid analog **3a-f** with either phenacyl bromide (**4a**), or 4-sulfonamidophenacyl bromide (**4b**), in the presence of triethylamine afforded the respective phenacyl phenylacetate product **5a-g**. Subsequent intramolecular cyclization [6] of **5a-g** using sodium hydride in dimethyl sulfoxide afforded the respective 3-(4-substituted-phenyl)-4-phenyl-2(5*H*)furanone analog **6a-g**. Chlorosulfonation [7] of the 3-(4-substituted-phenyl)-4-phenyl-2(5*H*)furanones **6a-f** by reaction with chlorosulfonic acid in chloroform, and then azidation [8] using NaN_3 in aqueous acetone gave the corresponding benzenesulfonyl azide product **7a-f** in 38-59% yield (Scheme 1).

Scheme 1[a]



[a] Reagents and conditions: (i) Et_3N, MeCN, 25 °C, 1 hour; (ii) NaH, DMSO, 25 °C, 1 hour; (iii) $ClSO_3H$, $CHCl_3$, 25 °C, 1 hour; (iv) NaN_3, aqueous acetone, 0 °C, 3 hours; (v) Concentrated NH_4OH, 95% EtOH, 25 °C, 1 hour.

Electrophilic chlorosulfonation of the 4-phenyl-2(5*H*)furanone possessing a C-3 phenyl *para*-methyl (**6a**), *para*-methoxy (**6b**) or *para*-ethoxy (**6c**) substituent occurred primarily at the *meta*-position of the C-4 phenyl ring. In contrast, a similar reaction of the C-3 phenyl (**6d**), 4-fluorophenyl (**6e**) and 4-chlorophenyl (**6f**) derivatives of 4-phenyl-2(5*H*)furanone resulted in chlorosulfonation at the *para*-position of the C-4 phenyl ring. Chlorosulfonation at the *meta*-position of the C-4 phenyl ring system is consistent with data obtained from a geometry optimized PM3 calculation [9] for 3-(4-methylphenyl)-4-phenyl-2(5*H*)furanone (**6a**), which showed that the electron density was highest at the *meta*-position (-0.102) relative to the *ortho* (-0.078) and *para* (-0.086) position of the C-4 ring. A similar PM3 calculation for 3-(4-fluorophenyl)-4-phenyl-2(5*H*)furanone (**6e**) produced data showing the electron density profile for the C-4 phenyl ring carbons was *meta* (-0.100) > *para* (-0.088) > *ortho* (-0.077). The reason why chlorosulfonation of 3-(4-fluorophenyl)-4-phenyl-2(5*H*)furanone (**6e**) undergoes chorosulfonation primarily at the *para*-position of the C-4 phenyl ring system is not clear.

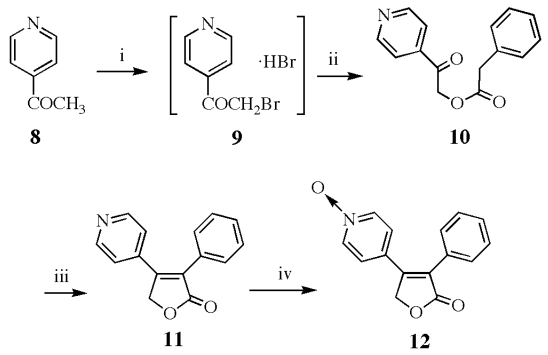
Two sets of reaction were performed to confirm the observation that electrophilic chlorosulfonation of 3,4-diphenyl-2(5*H*)furanone (**6d**) occurred at the *para*-position of the C-4 phenyl ring rather than on the C-3 phenyl ring. In this regard, it was established that 3-phenyl-4-(4-sulfonamidophenyl)-2(5*H*)furanone (**6g**) prepared from 4-sulfonamidophenacyl bromide (**4b**) was identical (^{1}H nmr) to the product (**6g**) prepared by reaction of the benzenesulfonyl chloride intermediate obtained from chlorosulfonation of **6d** with concentrated ammonium hydroxide (Scheme 1).

Isonicotinacyl bromide (**9**), prepared *in situ* by bromination [10] of 4-acetylpyridine (**8**), was condensed [5] with phenylacetic acid in the presence of triethylamine to afford isonicotinacyl phenylacetate (**10**) in 16% yield. Intramolecular cyclization [5] of isonicotinacyl phenylacetate (**10**) using triethylamine afforded 3-phenyl-4-(4-pyridyl)-2(5*H*)furanone (**11**) in 43% yield, which was then oxidized [11] using Oxone® (potassium peroxymonosulfate) to 4-(1-oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**) in 35% yield (Scheme 2).

Biological Results.

Rofecoxib analogs, having a SO_2N_3 group in place of the SO_2CH_3 pharmacophore at the *meta*- and *para*-positions of the C-4 phenyl ring were investigated to determine whether the sulfonylazido substituent is a suitable bioisostere with respect to selective COX-2 inhibition. The dipolar azido group is an attractive pharmacophore for use in drug design since it has the potential to undergo electrostatic interactions with the binding sites of enzymes or pharmacological receptors. In a previous study we reported [5] that the dipolar azido (N_3) moiety present in 4-(4-azidophenyl)-3-phenyl-2(5*H*)furanone (**2**) undergoes an electrostatic (ion-ion) interaction with arginine (Arg^{513}) in the COX-2 2º-pocket, indicating that dipolar azido substituent is a bioisostere of the *H*-bonding SO_2CH_3 pharmacophore present in rofecoxib [2]. Furthermore, the SO_2N_3 group has the potential to undergo dual *H*-bonding (sulfonyl oxygens) and electrostatic (ion-ion) interactions (dipolar N_3) suggesting that the SO_2N_3 moiety could serve as a new and alternative pharmacophore to the traditional

Scheme 2[a]



[a] Reagents and conditions: (i) Br_2, CCl_4, reflux 1 hour; (ii) $PhCH_2CO_2H$, Et_3N, MeCN, 25 °C, 1 hour; (iii) Et_3N, MeCN, reflux 2 hours; (iv) Oxone® (potassium peroxymonosulfate), MeOH, THF, H_2O, 25 °C, 15 hours

SO_2CH_3 or SO_2NH_2 *H*-bonding pharmacophores. Accordingly, the *para*-methylsulfonyl group of rofecoxib (**1**) was replaced by a *meta*-sulfonylazido group to prepare the 3-(4-methyl, 4-methoxy, or 4-ethoxyphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanones (**7a-c**). *In vitro* COX-1/COX-2 enzyme inhibition studies for 3-(4-methylphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7a**) and 4-(1-oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**) showed that these two compounds did not inhibit the COX-1 or COX-2 isozyme. This latter result shows that the 1-oxido-4-pyridyl moiety is not a suitable replacement for the methanesulfonylphenyl substituent present in rofecoxib with respect to COX-2 inhibition. Similar COX-1/COX-2 enzyme inhibition studies showed that 3-(4-methoxyphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7b**) inhibited COX-1 selectively (COX-1 IC_{50} = 7.32 μM; COX-2 IC_{50} > 100 μM) (Table 1). Replacement of the *para*-methylsulfonyl group of rofecoxib (**1**) by a *para*-sulfonylazido group provided 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**) and 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**). *In vitro* COX enzyme inhibition studies showed that 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**) inhibited COX-1 selectively (COX-1 IC_{50} = 0.6659 μM; COX-2 IC_{50} > 100 μM) and 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**) inhibited both isozymes (COX-1 IC_{50} = 0.8494 μM; COX-2 IC_{50} = 1.7661 μM) (Table 1). A molecular modeling study was therefore performed where 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**) was docked in the active site of the murine COX-2 isozyme in order to explain its failure to inhibit COX-2. This docking experiment showed that the linear azido component of the SO_2N_3 moiety is orientated towards a hydrophobic pocket at the top of the binding site near Try^{387} and Tyr^{385}, and that the terminal *N*-atom of the sulfonylazido group is about 4.16 Å from the O*H* of Tyr^{385} and about 4.23 Å from the O*H* of Ser^{530}. The *O*-atom of sulfonylazido group is interacting with Arg^{120} (2.14 Å, *H*-bonding interaction) at the mouth of the active site. The unsubstituted phenyl ring is orientated towards His^{90} and Tyr^{355} which is close to the entrance of the secondary pocket. In the 2º-pocket, Gln^{192} is interacting with the *O*-atom of the carbonyl group (2.79 Å, *H*-bonding interaction) and the *O*-atom of the central furanone ring (2.21 Å, *H*-bonding interaction). Recent studies

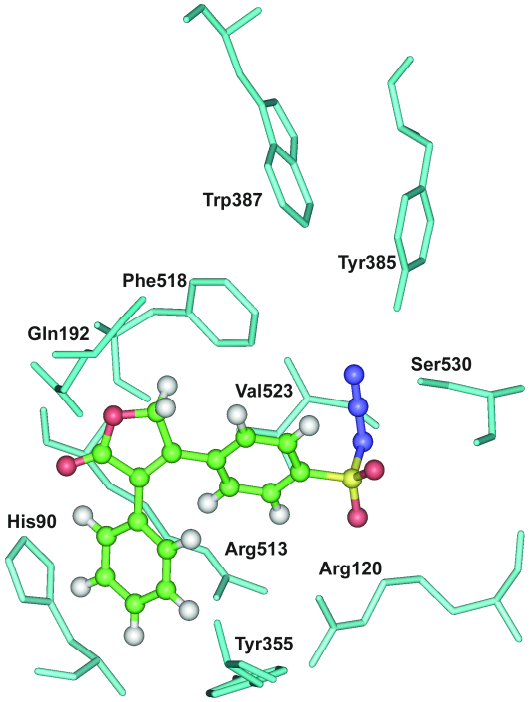
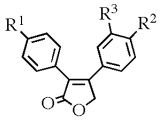


Figure 2. Docking 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**) (ball and stick) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

Table 1

In vitro COX-1 and COX-2 Enzyme Inhibition Data



Compd	R^1	R^2	R^3	IC_{50} (μM)[a] COX-1	IC_{50} (μM)[a] COX-2	COX-2 S.I.[b]
7a	Me	H	SO_2N_3	>100	>100	—
7b	OMe	H	SO_2N_3	7.32	>100	<0.073
7d	H	SO_2N_3	H	0.6659	>100	<0.006
7e	F	SO_2N_3	H	0.8494	1.7661	0.4809
12	H	N-oxide	H	>100	>100	—
Rofecoxib	H	SO_2CH_3	H	>500	0.4279	>1168

[a] Values are mean values of two determinations acquired using an ovine COX-1/COX-2 assay kit, where the deviation from the mean is < 10% of the mean value; [b] *In vitro* COX-2 selectivity index (COX-1 IC_{50}/ COX-2 IC_{50}).

have reported the importance of ionic interactions between the COOH group of arylacetic acid NSAIDs with Arg^{120} at the mouth of the binding site, and its critical role in COX-1 inhibition [12,13]. The COX-1 selectivity displayed by 3-phenyl-4-(4-sufonylazidophenyl)-2(5*H*)furanone (**7d**) is attributed to the fact that the sulfonyl component of the sulfonylazido group is interacting with Arg^{120} near the entrance to the binding site rather than insertion into the 2°-pocket of COX-2 that is necessary for selective COX-2 inhibition. In contrast, docking 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**) in the active site of COX-2 showed that the SO_2N_3 substituent is interacting with 2°-pocket amino acid residues such that the terminal *N*-atom of the sulfonylazido group is about 5.0 Å from the N*H*$_2$ of Gln^{192} and about 7.34 Å (weak electrostatic interaction) from the guanidino group of Arg^{513}. The sulfonyl *O*-atoms are interacting with the N*H*$_2$ of Gln^{192} (2.09 Å, *H*-bonding interaction) and amide hydrogen of Phe^{518} (1.99 Å, *H*-bonding interaction). In addition, a *H*-bonding interaction was observed between the carbonyl *O*-atom of the central furanone ring and the O*H* of Ser^{530} (2.33 Å), whereas the distance between the *O*-atom of central furanone ring and the NH_2 (guanidino) group of Arg^{120} at the mouth of the binding site was about 3.75 Å. The 4-fluoro-substituted phenyl ring is orientated towards a hydrophobic pocket comprised of Try^{387}, Tyr^{385} and Ser^{530} with the *F*-atom about 5.01 Å from the O*H* of Tyr^{385}. The results from these molecular modeling (docking) studies are consistent with the observations that 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**), but not 3-phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**), is able to inhibit the COX-2 isozyme. In this regard, the presence of the *para*-fluoro substituent (**7e**), relative to a *para*-hydrogen substituent (**7d**, inactive COX-2 inhibitor), plays a role in orienting **7e** more favorably within the COX-2 binding site, and is in agreement with the known structure-activity relationship that a *para*-fluorophenyl moiety often increases COX-2 selectivity [14].

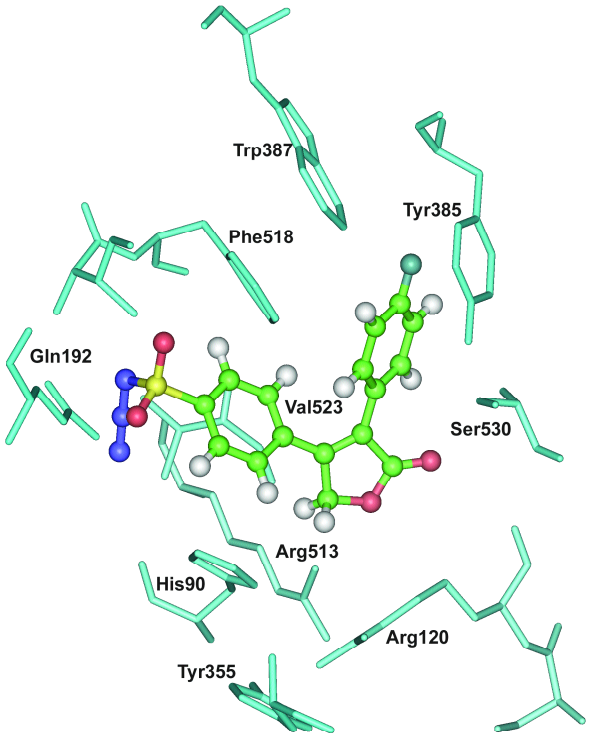


Figure 3. Docking 3-(4-fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**) (ball and stick) in the active site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

EXPERIMENTAL

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. Nuclear Magnetic Resonance (^{1}H nmr, ^{13}C nmr) spectra were recorded on a Bruker AM-300 spectrometer. ^{13}C NMR spectra were acquired using the *J* modulated spin echo technique where methyl and methine carbons appear as positive peaks and methylene and quarternary carbon resonances appear as negative peaks. Docking studies were performed using Insight II software Version 2000.1 (Accelrys Inc.) running on a Silicon Graphics Octane 2 R14000A workstation. The coordinates of the X-ray crystal structure of the selective COX-2 inhibitor SC-558 bound to the murine COX-2 enzyme was obtained from the RCSB Protein Data Bank (1cx2) and hydrogens were added. The ligand molecules were constructed using the Builder module and were energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The energy minimized ligands were superimposed on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The resulting structure (ligand-enzyme assembly) was minimized using the Discover module for 5000 iterations or until an RMSD of 0.05 Å was reached using the extensive systematic force field (ESFF). Further optimization of the ligand-enzyme complex was obtained using the Affinity command in the Docking module of Insight II by defining subsets of the enzyme such that residues within 10 Å of the ligand were allowed to relax, while the rest of the enzyme residues were fixed. The optimal binding orientation was achieved by utilizing 300 steps of steepest descent followed by the conjugate gradient method. The ESFF was employed for all docking purposes. These docked structures were very similar to the minimized structures obtained initially. The qualities of docked structures were evaluated by measuring the intermolecular energy of the ligand-enzyme assembly.

Elemental analysis was performed for C, H and N (Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta). Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70-230 mesh). The previously reported 4-sulfonamidophenacyl bromide (**4b**) [15], phenacyl 4-substituted-phenylacetates **5b-e** [16,17] and 3-(4-substituted-phenyl)-4-phenyl-2(5*H*)furanones **6b-e** [16,17] were prepared using literature methods [5, 6, 15] with slight modifications. All other reagents were purchased from the Aldrich Chemical Company (Milwaukee, WI), which were used without further purification.

Phenacyl 4-Methylphenylacetate (**5a**).

General Procedure.

Phenacyl bromide (**4a**, 1.99 g, 10.0 mmol) was added slowly to a solution of 4-methylphenylacetic acid (**3a**, 1.5 g, 10.0 mmol) in acetonitrile (100 mL) containing triethylamine (10 mL, 71.7 mmol) at 25 ºC. The reaction was allowed to proceed with stirring for 1 hour at 25 ºC, the solvent was removed *in vacuo*, and water (40 mL) was added to the residue. Extraction with ethyl acetate (3 x 50 mL), washing the combined extracts with dilute hydrochloric acid (3 x 100 mL), drying the organic fraction (Na_2SO_4), and removal of the solvent *in vacuo* gave a residue that was purified by silica gel column chromatography using ethyl acetate-hexane (1:1, v/v) as eluant to afford **5a** (1.87 g, 70%) as a white solid; mp 48-50 ºC; ir (film): 3134, 3058 (CH_{arom}), 2942, 2838 ($CH_{aliphatic}$), 1746, 1705 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3), 3.80 (s, 2H, OCOCH_2), 5.36 (s, 2H, OCH_2CO), 7.16 (d, *J* = 7.9 Hz, 2H, 4-methylphenyl H-3, H-5), 7.25 (d, *J* = 7.9 Hz, 2H, 4-methylphenyl H-2, H-6), 7.46-7.64 (m, 3H, phenyl H-3, H-4, H-5), 7.91 (d, *J* = 7.5 Hz, 2H, phenyl H-2, H-6).

Anal. Calcd. for $C_{17}H_{16}O_3 \cdot 1/4H_2O$: C, 74.83; H, 6.04. Found: C, 75.07; H, 6.28.

Compounds **5b-e** [16,17] and **5f** were prepared using a similar procedure to that described above, where **3b-f** were used in place of **3a**. Compound **5g** was also prepared in an identical manner from the reaction of 4-sulfonamidophenacyl bromide (**4b**) [15] with phenylacetic acid **3d**. The physical and spectral data of **5f-g** are listed below.

Phenacyl 4-Chlorophenylacetate (**5f**).

Compound **5f** was obtained as a brown syrup in 72% yield; ir (film): 3124, 3116 (CH_{arom}), 2918 ($CH_{aliphatic}$), 1746, 1688 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.80 (s, 2H, OCOCH_2), 5.37 (s, 2H, OCH_2CO), 7.21-7.30 (m, 4H, 4-chlorophenyl hydrogens), 7.48 (dd, *J* = 7.3, 7.3 Hz, 2H, phenyl H-3, H-5), 7.62 (dd, *J* = 7.3, 7.3 Hz, 1H, phenyl H-4), 7.90 (d, *J* = 7.3 Hz, 2H, phenyl H-2, H-6).

Anal. Calcd. for $C_{16}H_{13}ClO_3 \cdot 1/4H_2O$: C, 65.53; H, 4.60. Found: C, 65.22; H, 4.36.

4-Sulfonamidophenacyl Phenylacetate (**5g**).

Compound **5g** was obtained as a pale yellow solid in 63% yield; mp 120-122 ºC; ir (film) 3402, 3292 (NH_2), 3003 (CH_{arom}), 2907 ($CH_{aliphatic}$), 1739, 1657 (C=O), 1350, 1140 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.92 (s, 2H, OCOCH_2), 5.63 (s, 2H, OCH_2CO), 7.31-7.45 (m, 5H, phenyl hydrogens), 7.66 (s, 2H, NH_2), 8.04 and 8.20 (two d, *J* = 8.5 Hz, 2H each, 4-sulfonamidophenyl H-3, H-5 and 4-sulfonamidophenyl H-2, H-6).

Anal. Calcd. for $C_{16}H_{15}NO_5S$: C, 57.65; H, 4.54; N, 4.20. Found: C, 58.03; H, 4.57; N, 4.02.

3-(4-Methylphenyl)-4-phenyl-2(5*H*)furanone (**6a**).

General Procedure.

A solution of phenacyl 4-methylphenylacetate (**5a**, 1.34 g, 5.0 mmol) in dimethyl sulfoxide (20 mL) was added drop wise to a stirred suspension of sodium hydride (0.3 g, 12.5 mmol) in dimethyl sulfoxide (5 mL) at 25 ºC. After stirring for 1 hour at 25 ºC, the reaction mixture was poured into water (20 mL) and extracted with ethyl acetate (3 x 25 mL). The combined extracts were washed with water, and dried over sodium sulfate. Removal of the solvent *in vacuo* gave a residue, which was purified by silica gel column chromatography using ethyl acetate-hexane (1:1, v/v) as eluant to afford **6a** (0.8 g, 64%) as yellow needles; mp 115-117 ºC; ir (film): 3127, 3051 (CH_{arom}), 2928, 2873 ($CH_{aliphatic}$), 1746 (furanone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.38 (s, 3H, CH_3), 5.17 (s, 2H, CH_2), 7.19 (d, *J* = 7.5 Hz, 2H, 4-methylphenyl H-3, H-5), 7.33-7.47 (m, 7H, 4-methylphenyl H-2, H-6; phenyl hydrogens).

Anal. Calcd. for $C_{17}H_{14}O_2 \cdot 1/3H_2O$: C, 79.66; H, 5.72. Found: C, 79.69; H, 5.71.

The known compounds **6b-e** [15,16] and **6f-g** were prepared using the procedure described above, where **5b-g** were used in place of **5a**. The physical and spectral data for **6f-g** are listed below.

3-(4-Chlorophenyl)-4-phenyl-2(5*H*)furanone (**6f**).

Compound **6f** was obtained as a yellow syrup in 66% yield; ir (film): 3130, 3070 (CH_{arom}), 2972 ($CH_{aliphatic}$), 1757 (furanone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.18 (s, 2H, CH_2), 7.30-7.44 (m, 9H, phenyl and 4-chlorophenyl hydrogens).

Anal. Calcd. for $C_{16}H_{11}ClO_2 \cdot 1/7H_2O$: C, 70.31; H, 4.12. Found: C, 70.47; H, 4.04.

3-Phenyl-4-(4-sulfonamidophenyl)-2(5*H*)furanone (**6g**).

Method 1.

Compound **6g** was obtained as a pale yellow solid in 74% yield; mp 248-250 ºC; ir (film) 3430, 3230 (NH_2), 3008 (CH_{arom}), 2925 ($CH_{aliphatic}$), 1740 (furanone CO), 1340, 1140 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.43 (s, 2H, CH_2), 7.36-7.42 (m, 5H, phenyl hydrogens), 7.44 (s, 2H, NH_2), 7.52 (d, *J* = 8.2 Hz, 2H, 4-sulfonamidophenyl H-2, H-6), 7.85 (d, *J* = 8.2 Hz, 2H, 4-sulfonamidophenyl H-3, H-5).

Anal. Calcd. for $C_{16}H_{13}NO_4S$: C, 60.94; H, 4.16; N, 4.44. Found: C, 60.62; H, 3.92; N, 4.37.

3-Phenyl-4-(4-sulfonamidophenyl)-2(5*H*)furanone (**6g**).

Method 2.

Chlorosulfonic acid (1.5 mL, 22.5 mmol) was added drop wise to a solution of 3,4-diphenyl-2(5*H*)furanone (**6d**, 0.59 g, 2.5 mmol) in chloroform (1.5 mL) at –5 °C with vigorous stirring. After removing the cooling bath, the reaction was allowed to proceed for 1 hour at 25 ºC, and the mixture was poured into crushed ice (15 g) very slowly. Extraction with ethyl acetate (3 x 20 mL), washing the combined organic extracts with water, drying the organic fraction (Na_2SO_4), and removal of the solvent *in vacuo* afforded the corresponding sulfonyl chloride derivative as a brown syrup (0.80 g). Concentrated ammonium hydroxide (8 mL) was added to a solution of this sulfonyl chloride derivative in 95% ethanol (5 mL), and the reaction was allowed to proceed with stirring for 1 hour at 25 ºC. Removal of the solvent *in vacuo* gave a residue that was purified by silica gel column chromatography using ethyl acetate-hexane (1:4, v/v) as eluant to give 3-phenyl-4-(4-sulfonamidophenyl)-2(5*H*)furanone (**6g**, 0.42 g, 54%) as a pale yellow solid, which showed identical mp, ir and ^1H nmr data with the product obtained from method 1.

3-(4-Methylphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7a**).

General Procedure.

Chlorosulfonic acid (1.0 mL, 15 mmol) was added drop wise to a solution of 3-(4-methylphenyl)-4-phenyl-2(5*H*)furanone **(6a**, 0.42 g, 1.67 mmol) in chloroform (1 mL) at –5 ºC with vigorous stirring. The cooling bath was removed and the reaction was allowed to continue for 1 hour at 25 ºC at which time it was poured very slowly into crushed ice (10 g). Extraction with ethyl acetate (3 x 20 mL), washing the combined organic extracts with water (3 x 30 mL), and removal of the solvent *in vacuo* afforded the corresponding benzenesulfonyl chloride as a brown syrup, which was dissolved in acetone (2 mL). This solution was added drop wise to a stirred solution of sodium azide (0.065 g, 1.0 mmol) in aqueous acetone (2 mL) at –5 ºC and the reaction mixture was stirred for 3 hours at 0 ºC. The solvent was removed *in vacuo* and water (10 mL) was added to the residue. Extraction with ethyl acetate (3 x 15 mL), drying the combined extracts (Na_2SO_4) and removal of the solvent *in vacuo* gave a yellow syrup, which was purified by silica gel column chromatography using ethyl acetate-hexane (2:1, v/v) as eluant to afford **7a** (0.15 g, 49%) as yellow needles; mp 108-110 ºC; ir (film): 3105, 3050 (CH_{arom}), 2950, 2825 ($CH_{aliphatic}$), 2113 (N_3), 1733 (furanone CO), 1368, 1153 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.70 (s, 3H, C*H*$_3$), 5.22 (s, 2H, C*H*$_2$), 7.31 (d, *J* = 7.6 Hz, 2H, 4-methylphenyl H-3, H-5), 7.41 (d, *J* = 7.6 Hz, 2H, 4-methylphenyl H-2, H-6), 7.40-7.49 (m, 2H, 3-sulfonylazidophenyl H-5, H-6), 7.76 (dd, 1H, *J* = 7.9, 1.8 Hz, 3-sulfonylazidophenyl H-4), 8.06 (d, *J* = 1.8 Hz, 2H, 3-sulfonylazidophenyl H-2); ^{13}C nmr (deuteriochloroform): δ 20.34 (CH_3), 70.82 (CH_2), 123.85 (furanone C-3), 127.28, 129.34 (4-methylphenyl C-2, C-6; C-3, C-5), 129.98, 131.14, 133.50, 135.20 (3-sulfonylazidophenyl C-5, C-6, C-4, C-2), 128.97, 137.26, 130.12, 138.86 (4-methylphenyl C-1, C-4; 3-sulfonylazidophenyl C-1, C-3), 158.05 (furanone C-4), 172.45 (CO).

Anal. Calcd. for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82. Found: C, 57.44; H, 3.93; N, 11.59.

Compounds **7b-f** were prepared using similar chlorosulfonation and then azidation reactions as described above, where **6b-f** were used in place of **6a**. The physical and spectral data for **7b-f** are listed below.

3-(4-Methoxylphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7b**).

Compound **7b** was obtained as a pale yellow solid in 49% yield; mp 163-165 ºC; ir (film): 3090, 3010 (CH_{arom}), 2990, 2880 ($CH_{aliphatic}$), 2135 (N_3), 1740 (furanone CO), 1345, 1145 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.07 (s, 3H, OC*H*$_3$), 5.19 (s, 2H, C*H*$_2$), 7.14 (d, *J* = 8.8 Hz, 1H, 3-sulfonylazidophenyl H-6), 7.30 (d, *J* = 7.9 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.33-7.50 (m, 3H, 4-methoxyphenyl H-2, H-6; 3-sulfonylazidophenyl H-5), 7.81 (dd, *J* = 9.0, 2.1 Hz, 1H, 3-sulfonylazidophenyl H-4), 7.96 (d, *J* = 2.1 Hz, 1H, 3-sulfonylazidophenyl H-2); ^{13}C nmr (deuteriochloroform): δ 56.61 (OCH_3), 70.78 (CH_2), 112.71 (4-methoxyphenyl C-3, C-5), 122.86 (4-methoxyphenyl C-1), 123.59 (furanone C-3), 127.24, 131.10, 131.19, 137.10 (3-sulfonylazidophenyl C-5, C-6, C-4, C-2), 129.34 (4-methoxyphenyl C-2, C-6), 127.92, 130.18 (3-sulfonylazidophenyl C-1, C-3), 157.01, 157.17 (furanone C-4, 4-methoxyphenyl C-4), 172.68 (CO).

Anal. Calcd. for $C_{17}H_{13}N_3O_5S$: C, 54.98; H, 3.53; N, 11.31. Found: C, 54.99; H, 3.59; N, 11.34.

3-(4-Ethoxylphenyl)-4-(3-sulfonylazidophenyl)-2(5*H*)furanone (**7c**).

Compound **7c** was obtained as a yellow solid in 59% yield; mp 168-170 ºC; ir (film): 3050 (CH_{arom}), 2950, 2850 ($CH_{aliphatic}$), 2150 (N_3), 1750 (furanone CO), 1340, 1160 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.56 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 4.31 (q, *J* = 7.3 Hz, 2H, ethoxy C*H*$_2$), 5.18 (s, 2H, C*H*$_2$), 7.11 (d, *J* = 8.7 Hz, 1H, 3-sulfonylazidophenyl H-6), 7.30 (d, *J* = 8.5 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.37-7.47 (m, 3H, 4-ethoxyphenyl H-2, H-6; 3-sulfonylazidophenyl H-5), 7.77 (dd, *J* = 8.4, 2.2 Hz, 1H, 3-sulfonylazidophenyl H-4), 7.95 (d, *J* = 2.2 Hz, 1H, 3-sulfonylazidophenyl H-2); ^{13}C nmr (deuteriochloroform): δ 14.77 (CH_3), 65.81 (ethoxy CH_2), 70.78 (CH_2), 113.66 (4-ethoxyphenyl C-3, C-5), 122.65 (4-ethoxyphenyl C-1), 123.64 (furanone C-3), 127.24, 131.04, 131.37, 137.11 (3-sulfonylazidophenyl C-5, C-6, C-2, C-4), 129.34 (4-ethoxyphenyl C-2, C-6), 128.04, 130.24 (3-sulfonylazidophenyl C-1, C-3), 156.64, 157.07 (furanone C-4, 4-ethoxyphenyl C-4), 172.71 (CO)

Anal. Calcd. for $C_{18}H_{15}N_3O_5S•1/3H_2O$: C, 55.23; H, 4.00; N, 10.73. Found: C, 55.09; H, 3.66; N, 10.75.

3-Phenyl-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7d**).

Compound **7d** was obtained as a pale yellow solid in 57% yield; mp 120-122 ºC; ir (film): 3120, 3050 (CH_{arom}), 2950, 2890 ($CH_{aliphatic}$), 2115 (N_3), 1750 (furanone CO), 1350, 1160 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.24 (s, 2H, C*H*$_2$), 7.26-7.39 (m, 2H, phenyl H-2, H-6), 7.44-7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.70 (d, *J* = 8.5 Hz, 2H, 4-sulfonylazidophenyl H-2, H-6), 7.85 (d, *J* = 8.5 Hz, 2H, 4-sulfonylazidophenyl H-3, H-5); ^{13}C nmr (deuteriochloroform): δ 70.91 (CH_2), 124.05 (furanone C-3), 127.33, 127.43, 129.44, 130.56, 131.40 (4-sulfonylazidophenyl, C-2, C-6; C-3, C-5 and phenyl C-2, C-6; C-4; C-3, C-5), 136.97 (phenyl C-1), 129.89, 138.39 (4-sulfonylazidophenyl C-4, C-1), 159.34 (furanone C-4), 172.23 (CO).

Anal. Calcd. for $C_{16}H_{11}N_3O_4S$: C, 56.30; H, 3.25; N, 12.31. Found: C, 56.30; H, 3.14; N, 12.70.

3-(4-Fluorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7e**).

Compound **7e** was obtained as a pale yellow solid in 44% yield; mp 134-136 ºC; ir (film): 3115, 3090 (CH_{arom}), 2980, 2905, 2850 ($CH_{aliphatic}$), 2125 (N_3), 1745 (furanone CO), 1350, 1150 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.20 (s, 2H, C*H*$_2$), 7.11 (d, J_{HCCF} = 8.5 of d, J_{HCCH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.40 (d, J_{HCCH} = 8.5 of d, J_{HCCCF} = 5.4 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.53 (d, *J* = 8.2 Hz, 2H, 4-sulfonylazidophenyl H-2, H-6), 7.96 (d, *J* = 8.2 Hz, 2H, 4-sulfonylazidophenyl H-3, H-5); ^{13}C nmr (deuteriochloroform): δ 70.28 (CH_2), 116.25 (d, J_{CCF} = 22.0 Hz, 4-fluorophenyl C-3, C-5), 124.88 (furanone C-3), 128.17, 128.62 (4-sulfonylazidophenyl C-2, C-6; C-3, C-5), 128.49 (4-fluorophenyl C-1), 131.01 (d, J_{CCCF} = 13.1 Hz, 4-fluorophenyl C-2, C-6), 137.11, 139.89 (4-sulfonylazidophenyl C-4, C-1), 152.76 (furanone C-4), 163.27 (d, J_{CF} = 250.4 Hz, 4-fluorophenyl C-4), 172.02 (CO).

Anal. Calcd. for $C_{16}H_{10}FN_3O_4S$: C, 53.48; H, 2.81; N, 11.69. Found: C, 53.76; H, 2.66; N, 11.56.

3-(4-Chlorophenyl)-4-(4-sulfonylazidophenyl)-2(5*H*)furanone (**7f**).

Compound **7f** was obtained as a yellow syrup in 38% yield; ir (film): 3050 (CH_{arom}), 2990, 2850 ($CH_{aliphatic}$), 2110 (N_3), 1740

(furanone CO), 1350, 1150 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.20 (s, 2H, CH_2), 7.36 (d, *J* = 6.5 Hz, 2H, 4-chlorophenyl H-3, H-5), 7.40 (d, *J* = 6.5 Hz, 2H, 4-chlorophenyl H-2, H-6), 7.55 (d, *J* = 8.2 Hz, 2H, 4-sulfonylazidophenyl H-2, H-6), 7.96 (d, *J* = 8.2 Hz, 2H, 4-sulfonylazidophenyl H-3, H-5); ^{13}C nmr (deuteriochloroform): δ 70.34 (CH_2), 127.28 (furanone C-3), 127.28, 128.39, 129.35, 130.47 (4-sulfonylazidophenyl C-2, C-6; C-3, C-5 and 4-chlorophenyl C-3, C-5; C-2, C-6), 128.22 (4-chlorophenyl C-1), 135.86, 136.97, 140.01 (4-chlorophenyl C-4; 4-sulfonylazidophenyl C-4, C-1), 153.23 (furanone C-4), 170.0 (CO).

Anal. Calcd. for $C_{16}H_{10}ClN_3O_4S$•1/3H_2O: C, 50.33; H, 2.79; N, 11.00. Found: C, 50.66; H, 2.58; N, 10.59.

Isonicotinacyl Phenylacetate (**10**).

Bromine (0.5 mL, 9.97 mmol) was added drop wise to a solution of 4-acetylpyridine (**8**, 1.21 g, 10.0 mmol) in carbon tetrachloride (50 mL) and the reaction mixture was refluxed for 1 hour. After cooling to 25 ºC, the solvent was evaporated to give isonicotinacyl bromide (**9**) as a hydrobromide salt, which was added slowly with stirring to a solution of phenylacetic acid (1.36 g, 10.0 mmol) in acetonitrile (125 mL) containing triethylamine (11 mL, 78.9 mmol) at 25 ºC. The reaction was allowed to proceed for 1 hour with stirring at 25 ºC, the solvent was removed *in vacuo*, and water (50 mL) was added to the residue. Extraction with ethyl acetate (3 x 60 mL), washing the combined extracts with water (3 x 100 mL), drying the organic fraction (Na_2SO_4), and removal of the solvent *in vacuo* gave a residue that was purified by silica gel column chromatography using ethyl acetate as eluant to afford isonicotinacyl phenylacetate (**10**, 0.42 g, 16%) as a brown syrup; ir (film): 3017 (CH_{arom}), 2920 ($CH_{aliphatic}$), 1703, 1752 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.73 (s, 2H, OCOCH_2), 5.21 (s, 2H, OCH_2CO), 7.21-7.27 (m, 5H, phenyl hydrogens), 7.57 (d, *J* = 4.6 Hz, 2H, isonicotinyl H-3, H-5), 8.73 (d, *J* = 4.6 Hz, 2H, isonicotinyl H-2, H-6).

Anal. Calcd. for $C_{15}H_{13}NO_3$·1/4H_2O: C, 69.34; H, 5.20; N, 5.38. Found: C, 69.37; H, 5.60; N, 5.32.

3-Phenyl-4-(4-pyridyl)-2(5*H*)furanone (**11**).

Triethylamine (2.0 mL, 14.5 mmol) was added drop wise to a solution of isonicotinacyl phenylacetate (**10**, 0.26 g, 1.0 mmol) in acetonitrile (20 mL) and the reaction mixture was refluxed for 2 hours. Removal of the solvent *in vacuo* gave a residue, to which water (20 mL) was added. Extraction with ethyl acetate (3 x 30 mL), washing the combined extracts with water (3 x 50 mL), drying the organic fraction (Na_2SO_4), and removal of the solvent gave a residue that was purified by silica gel column chromatography using ethyl acetate as eluant to give 3-phenyl-4-(4-pyridyl)-2(5*H*)furanone (**11**, 0.1 g, 43%) as a yellow solid; mp 124-126 ºC; ir (film): 3039 (CH_{arom}), 2910 ($CH_{aliphatic}$), 1741 (furanone CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 5.18 (s, 2H, CH_2), 7.19 (d, *J* = 4.6 Hz, 2H, 4-pyridyl H-3, H-5), 7.38-7.43 (m, 5H, phenyl hydrogens), 8.64 (d, *J* = 4.6 Hz, 2H, 4-pyridyl H-2, H-6).

Anal. Calcd. for $C_{15}H_{11}NO_2$•1/12H_2O C, 75.45; H, 4.67; N, 5.86. Found: C, 75.44; H, 4.43; N, 5.64.

4-(1-Oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**).

A solution of Oxone® (potassium peroxymonosulfate) (1.28 g, 2.08 mmol) in water (6 mL) was added slowly to a solution of 3-phenyl-4-(4-pyridyl)-2(5*H*)furanone (**11**, 0.08 g, 0.66 mmol) in methanol (2 mL) and THF (2 mL) at 0 ºC. This reaction mixture was stirred for 15 hours at 25 ºC, the solvent was removed *in vacuo* and water (10 ml) was added to the residue. Extraction with ethyl acetate (3 x 20 mL), washing the combined extracts with water (3 x 30 mL), drying the organic fraction (sodium sulfate), and removal of the solvent *in vacuo* gave a residue that was purified by silica gel column chromatography using ethyl acetate as eluant to afford 4-(1-oxido-4-pyridyl)-3-phenyl-2(5*H*)furanone (**12**, 0.03 g, 35%) as a white solid; mp 175-177 ºC; ir (film): 3104, 3008 (CH_{arom}), 1756 (furanone CO), 1478 (NO) cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 5.21 (s, 2H, CH_2), 7.24 (d, *J* = 7.0 Hz, 2H, 4-pyridyl-1-oxido H-3, H-5), 7.28-7.38 (m, 5H, phenyl hydrogens), 8.04 (d, *J* = 7.0 Hz, 2H, 4-pyridyl-1-oxido H-2, H-6); ^{13}C nmr (deuteriochloroform + DMSO-d_6): δ 68.75 (CH_2), 123.50, 127.72, 127.79, 128.11 (4-pyridyl-1-oxido C-3, C-5; phenyl carbons), 125.77 (furanone C-3), 126.50, 128.32 (4-pyridyl-1-oxido C-4; phenyl C-1), 138.12 (4-pyridyl-1-oxido C-2, C-6), 150.43 (furanone C-4), 171.18 (CO).

Anal. Calcd. for $C_{15}H_{11}NO_3$•1/8H_2O: C, 70.50; H, 4.40, N, 5.47. Found: C, 70.26; H, 4.37, N, 5.38.

Cyclooxygenase (COX) Inhibition Assays.

The *in vitro* ability of test compounds to inhibit COX-1 and COX-2 was determined using a COX (ovine) inhibition screening kit (catalog no. 560101, Cayman Chemical, Ann Arbor, MI) according to the method previously reported [18].

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REFERENCES AND NOTES

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[1] T. D. Penning, J. J. Talley, S. R. Bertenshaw, J. S. Carter, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rogers, S. S. Yu, G. D. Anderson, E. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang and P. C. Isakson, *J. Med. Chem.*, **40**, 1347 (1997).

[2] P. Prasit, Z. Wang, C. Brideau, C.-C. Chan, S. Charleson, W. Cromlish, D. Ethier, J. F. Evans, A. W. F. Hutchinson, J. Y. Gauthier, R. Gordon, J. Guay, M. Gresser, S. Kargman, B. Kennedy, Y. Leblanc, S. Léger, J. Manchini, G. P. O'Neill, M. Ouellet, M. D. Percival, H. Perrier, D. Riendeau, I. Rodger, P. Tagari, M. Thérein, P. Vickers, E. Wong, L.-J. Xu, R. N. Young and R. Zambani, *Bioorg. Med. Chem. Lett.*, **9**, 1773 (1999).

[3] O. Llorens, J. J. Perez, A. Palomer and D. Mauleon, *Bioorg. Med. Chem. Lett.*, **9**, 2779 (1999).

[4] R. M. Garavito and D. L. DeWitt, *Biochim. Biophys. Acta*, **1441**, 278 (1999)

[5] A. G. Habeeb, P. N. P. Rao and E. E. Knaus, *J. Med. Chem.*, **44**, 3039 (2001).

[6] M. A. Rahim, P. N. P. Rao and E. E. Knaus, *Bioorg. Med. Chem. Lett.*, **12**, 2753 (2002).

[7] H. Hashimoto, K. Imamura, J.-I. Haruta and K. Wakitani, *J. Med. Chem.*, **45**, 1511 (2002).

[8] J. E. Leffler and Y. Tsuno, *J. Org. Chem.*, **28**, 902 (1963).

[9] Alchemy 2000 (program), Version 2.0, Tripos Inc., St. Louis, MO, USA.

[10] G. Sarodnick and G. Kempter, *Pharmazie*, **40**, 384 (1985).
[11] R. J. Kennedy and A. M. Stock, *J. Org. Chem*., **25**, 1901 (1960).
[12] G. M. Greig, D. A. Francis, J. P. Falgueyret, M. Ouellet, M. D. Percival, P. Roy, C. Bayly, J. A. Mancini and G. P. O'neill, *Mol. Pharmacol.*, **52**, 829 (1997).
[13] B. S. Selinsky, K. Gupta, C. T. Sharkey and P. J. Loll, *Biochemistry*, **40**, 5172 (2001).
[14] J. J. Talley, *Progress in Medicinal Chemistry*, **36**, 201 (1999).
[15] Ferrania Societa Per Azioni, *Chem. Abstr.*, **67**, 91689 (1967).
[16] V. R. Pattabiraman, S. Padakanti, V. R. Veeramaneni, M. Pal and K. R. Yeleswarapu, *Synlett.*, **6**, 947 (2002).
[17] S. T. Vijayaraghavan and T. R. Balasubramanian, *Ind. J. Chem.*, **25B**, 760 (1986).
[18] A. G. Habeeb, P. N. P. Rao and E. E. Knaus, *Drug Dev. Res.*, **51**, 273 (2000).