A New Class of Acyclic 2-Alkyl-1,1,2-Triaryl (*Z*)-Olefins as Selective Cyclooxygenase-2 Inhibitors

Md. Jashim Uddin,[†] P. N. Praveen Rao,[†] Robert McDonald,[‡] and Edward E. Knaus*,[†]

Faculty of Pharmacy and Pharmaceutical Sciences, University of Alberta, Edmonton, Alberta, Canada T6G 2N8, and Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2

Received June 18, 2004

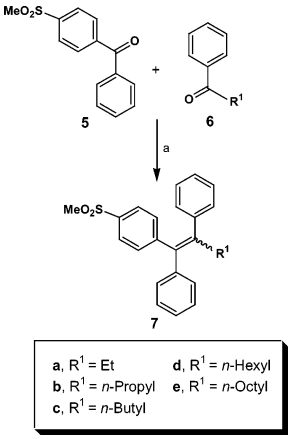
A new class of acyclic (*Z*)-2-alkyl-1,2-diphenyl-1-(4-methanesulfonylphenyl)ethenes (**7**) was designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1 and COX-2 isozyme inhibition structure−activity studies identified (*Z*)-1,2-diphenyl-1-(4-methanesulfonylphenyl)oct-1-ene (**7d**) as a potent COX-2 inhibitor (IC_{50} = 0.42 μM) with a high COX-2 selectivity index (SI > 234). In a carrageenan-induced rat paw edema assay, (*Z*)-**7d** exhibited excellent antiinflammatory activity (ID_{50} = 1.1 mg/kg). The molecular modeling and structure−activity data acquired indicate that (*Z*)-olefins having cis C-1 4-methanesulfonylphenyl and C-2 unsubstituted phenyl (or 4-acetoxyphenyl) substituents in conjunction with a C-1 phenyl ring and a C-2 alkyl substituent of appropriate length constitute a suitable template for the design of a novel class of acyclic (*Z*)-2-alkyl-1,1,2-triaryleth-1-ene COX-2 inhibitors.

Introduction

A number of tricyclic selective cyclooxygenase-2 (COX-2) inhibitors represented by celecoxib (**1**) and rofecoxib (**2**) are effective antiinflammatory and analgesic agents with reduced gastrointestinal (GI) toxicity profiles (see structures **1**−**4** in Chart 1, Supporting Information).[1,2] Tricyclic molecules possessing 1,2-diaryl substitution on a central heterocyclic, or carbocyclic, ring system represent a major class of selective COX-2 inhibitors. It is known that *cis*-stilbene derivatives which possess vicinal diaryl moieties along with a COX-2 pharmacophore such as SO_2Me or SO_2NH_2 at the para-position of one of the aromatic rings retains COX-2 inhibitory potency and selectivity (**3**).[3] In this regard, an acyclic triaryl olefin is an attractive target for the rational design of selective COX-2 inhibitors since the presence of a central C=C bond should provide the necessary geometry for the appropriately substituted vicinal diaryl rings to interact favorably with the COX-2 binding site. Accordingly, in a previous study, we showed that an appropriately substituted acyclic triaryl olefin (**4**) serves as a suitable template to design potent COX-2 selective inhibitors.[4] Some structurally related stilbenes derived from tamoxifen bearing a thiomethyl substituent exhibit anticancer activity.[5] We now report the design, synthesis and biological evaluation of a novel class of acyclic triaryl (*Z*)-olefins possessing an appropriately substituted *p*-SO_2Me COX-2 pharmacophore.

Chemistry. A Zn−$TiCl_4$-catalyzed McMurry reaction of 4-methanesulfonylbenzophenone **5**[6] and an alkanophenone (**6**, R^1 = Et, *n*-propyl, *n*-butyl, *n*-hexyl, *n*-octyl) afforded the target olefins **7** (R^1 = Et, *n*-propyl, *n*-butyl, *n*-hexyl, *n*-octyl) with predominant (*Z*)-selectivity (**7e**, R^1 = *n*-octyl, *Z:E* ratio = 4:1). The undesired homocoupled olefinic products formed in this reaction were separated from the desired cross-coupled mixture of (*Z*)- and (*E*)-olefins (**7a**−**e**). Subsequent fractional recrystallizations of the predominant (*Z*)-isomer from the (*Z*):(*E*) mixture of cross-coupled olefin (**7**) provided the respective target (*Z*)-olefin **7a**−**e** in 62−65% isolated yield (Scheme 1). The structures of the (*Z*)-olefin products were consistent with their spectral and microanalytical data. The absolute stereochemistry of (*Z*)-**7a** (R^1 = Et) was unambiguously confirmed by a single-crystal X-ray analysis (see Chart 1 in Supporting Information). The mechanism of this McMurry olefination reaction proceeds via a titanium-induced deoxygenation of the bidentate pinacolic intermediate that is formed by homolytic coupling of two radical anion species generated from reduction of carbonyl compounds.[7] Although the mechanism of (*Z*)-stereocontrol for this olefination reaction is not fully understood, it is plausible that there is a preferred orientation of the substituted phenyl ring of ketone **5** and the unsubstituted phenyl ring of ketone **6** in the transient titanium pinacolate, whereby these two rings are oriented on the same side by a weak interaction.[8] On the other hand,

Scheme 1[a]

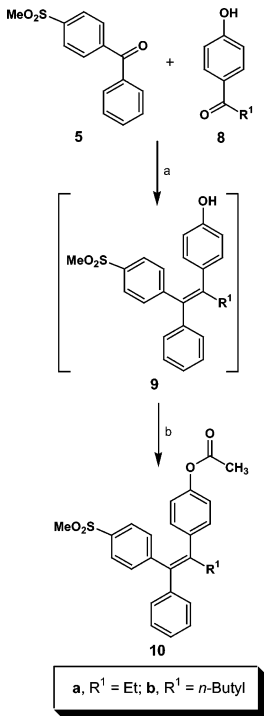


[a] Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 4.5 h.

* To whom correspondence should be addressed. Phone: 780-492-5993. Fax: 780-492-1217. E-mail: eknaus@pharmacy.ualberta.ca.
[†] Faculty of Pharmacy and Pharmaceutical Sciences.
[‡] Department of Chemistry.

10.1021/jm049523y CCC: $27.50
Published on Web 10/19/2004

Scheme 2[a]



[a] Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 4.5 h; (b) AcCl, TEA, ether, 25 °C, 1.5 h.

the intermediate (*Z*)-olefins **9** (R^1 = Et, *n*-butyl) were generated in situ using a (*Z*)-stereocontrolled McMurry reductive cross-coupling reaction[9] of 4-methanesulfonylbenzophenone **5** and a 4-hydroxyalkanophenone (**8**, R^1 = Et, *n*-butyl). Subsequent acetylation of intermediates **9** afforded the target (*Z*)-acetoxyphenyl products **10a**,**b** (R^1 = Et, *n*-butyl) in 62−67% overall yield (Scheme 2).[10] In regard to the stereochemical aspects of this latter (*Z*)-stereocontrolled olefination reaction, it has been proposed that the (*Z*)-isomer arises from a consecutive induction by the active Ti° surface to the polydentate pinacolic intermediate formed by a homolytic coupling of a radical anion species generated from reduction of the two carbonyl compounds,[11] prior to subsequent demetalation and deoxygenation reactions.[12] In this regard, the 'phenoxy-Ti-sulfone' induction plays the key role for (*Z*)-stereoselection by forcing the phenoxy and sulfone moieties to be positioned on the same side (cis) to each other.[9]

Results and Discussion

In a previous study we demonstrated that simple acyclic triaryl olefins exhibit selective COX-2 inhibition when (i) two geminal unsubstituted phenyl substituents are present at the C-1 position, (ii) a 4-methanesulfonylphenyl substituent is located at the C-2 position, and (iii) a *n*-alkyl substituent of appropriate chain length is attached to the C-2 position.[4] Initial structure−activity relationship (SAR) studies, where the length of the C-2 alkyl substituent was varied, indicated that maximal COX-2 inhibitory potency (IC_{50} = 0.014 μM) and selectivity (SI > 7142) was exhibited by 1,1-diphenyl-2-(4-methanesulfonylphenyl)hex-1-ene (**4**) having a C-2 *n*-butyl side chain.[4] This initial study has now been extended to include the design of a related group of olefinic regioisomers of compound **4** possessing (i) an absolute (*Z*)-stereochemistry, (ii) a 4-methanesulfonylphenyl ring located at the C-1 position, (iii) two vicinal unsubstituted phenyl rings present at the C-1 and C-2 positions, and (iv) a *n*-alkyl substituent of appropriate chain length attached to the C-2 position. In vitro COX-1 and COX-2 enzyme inhibition studies showed that (*Z*)-olefinic analogues possessing short hydrophobic alkyl side chains (**7a**, R^1 = Et; COX-2 IC_{50} = 3.2 μM, COX-1 IC_{50} > 100 μM; **7b**, R^1 = *n*-propyl; COX-2 IC_{50} = 2.8 μM, COX-1 IC_{50} > 100 μM) exhibited comparable activity profiles (Table 1). A similar enzyme inhibition assay showed that the olefin (*Z*)-**7c** (R^1 = *n*-butyl) was a nonselective COX inhibitor. As the alkyl substituent chain length was increased, COX-2 inhibitory potency and selectivity also increased substantially with (*Z*)-**7d** (R^1 = *n*-hexyl, COX-2 IC_{50} = 0.42 μM, COX-1 IC_{50} > 100 μM; COX-2 SI > 234), exhibiting a potency and selectivity similar to the reference drug rofecoxib (COX-2 IC_{50} = 0.5 μM, COX-1 IC_{50} > 100 μM; COX-2 SI > 200). A further increase in alkyl chain length provided (*Z*)-**7e** (R^1 = *n*-octyl, COX-1 IC_{50} > 100 μM, COX-2 IC_{50} 3.1 μM, COX-2 SI > 32.4) that showed a dramatic decrease in COX-2 potency and selectivity since it was 6-fold less potent and selective than rofecoxib. A molecular modeling study where the triaryl (*Z*)-olefin (*Z*)-**7d** (R^1 = *n*-hexyl) was docked in the COX-2 binding site showed (Figure 1) that (*Z*)-**7d** binds in the center of the primary binding site such that the C-1 4-methanesulfonylphenyl ring is oriented toward the COX-2 secondary pocket, and the *p*-SO_2Me pharmacophore is interacting with the amino acid residues lining the COX-2 binding site (Val^{523}, Phe^{518}, Gln^{192}, Arg^{513}, and His^{90}). One of the O-atoms of the SO_2Me group forms a hydrogen bond with the backbone N*H* of Phe^{518} (distance = 2.18 Å). In addition, a weak hydrogen bonding interaction was observed between the other O-atom of the SO_2Me moiety and the N*H* of His^{90} (distance = 4.01 Å). The unsubstituted C-2 phenyl ring that is cis to the C-1 *p*-$MeSO_2$-phenyl substituent is oriented toward the apex of the COX-2 primary binding site in the vicinity of Leu^{384}, Tyr^{385}, and Trp^{387} and about 5.9 Å from the *O*H of Ser^{530}. The C-2 *n*-hexyl chain is appropriately oriented in a hydrophobic region closer to the mouth of the COX-2 binding site comprised of Leu^{531}, Ile^{345}, Val^{349}, and Leu^{359} (distance < 5 Å). The C-1 unsubstituted phenyl ring, that is cis to the C-2 *n*-hexyl substituent, is oriented toward the mouth of the COX-2 binding site (Tyr^{355} and Arg^{120}). The distance between the center of the C-1 phenyl ring and the NH_2 of Arg^{120} is about 6.3 Å.

Our previous molecular modeling studies on the regioisomeric acyclic triaryl olefins possessing a *p*-SO_2Me COX-2 pharmacophore at the C-2 phenyl ring of the central C=C had shown that the C-2 *p*-SO_2Me COX-2 pharmacophore was oriented favorably within the COX-2 secondary pocket. In addition, due to the regioisomeric placement of the *p*-SO_2Me COX-2 pharmacophore, the C-2 *n*-alkyl chain was oriented toward a pocket comprised of Tyr^{355}, Arg^{120}, Leu^{359}, and Val^{349} closer to the mouth of the COX-2 active site.[4] It is significant to note that for this class of acyclic triaryl olefins, the regioisomeric placement of the *p*-SO_2Me pharmacophore either at the C-1 or C-2 position of the central C=C

Table 1. In Vitro COX-1/COX-2 Enzyme Inhibition Assay Data for (*Z*)-Olefins **7a**−**e**, **10a**,**b** and in Vivo Antiinflammatory and Analgesic Activity Assay Data for (*Z*)-Olefins **7a**, **7e**, and **10a**

						analgesic activity[d]	
compd	R^1	COX-1: IC_{50} (μM)[a]	COX-2: IC_{50} (μM)[a]	COX-2: SI[b]	AI activity:[c] ID_{50} (mg/kg)	% inhibition (30 min)	% inhibition (60 min)
(*Z*)-**7a**	Et	>100	3.2	>31	1.9	38.8 ± 6.8	50.0 ± 11.7
(*Z*)-**7b**	*n*-C_3H_7	>100	2.8	>35	–	–	–
(*Z*)-**7c**	*n*-C_4H_9	30	10	3	–	–	–
(*Z*)-**7d**	*n*-C_6H_{13}	>100	0.42	>234	1.1	33.3 ± 13.6	35.4 ± 19.3
(*Z*)-**7e**	*n*-C_8H_{17}	>100	3.1	>32	–	–	–
(*Z*)-**10a**	Et	0.25	0.05	5	1.3	60.0 ± 6.8	57.5 ± 5.6
(*Z*)-**10b**	*n*-C_4H_9	>100	1.1	>95	–	–	–
celecoxib	–	33.1	0.07	472	10.8	69.3 ± 12.1[e]	79.5 ± 2.0[e]
rofecoxib	–	>100	0.50	>200	–	–	–
aspirin	–	0.35	2.4	0.14	–	–	–

[a] The in vitro test compound concentration required to produce 50% inhibition of COX-1 or COX-2. The result (IC_{50}, μM) is the mean of two determinations. [b] Selectivity Index (SI) = COX-1 IC_{50}/COX-2 IC_{50}. [c] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as the ID_{50} value (mg/kg) at 3 h after oral administration of the test compound. [d] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as the mean % inhibition value ± SEM (n = 4) following a 5 mg/kg oral dose of the test compound. [e] 50 mg/kg oral dose.

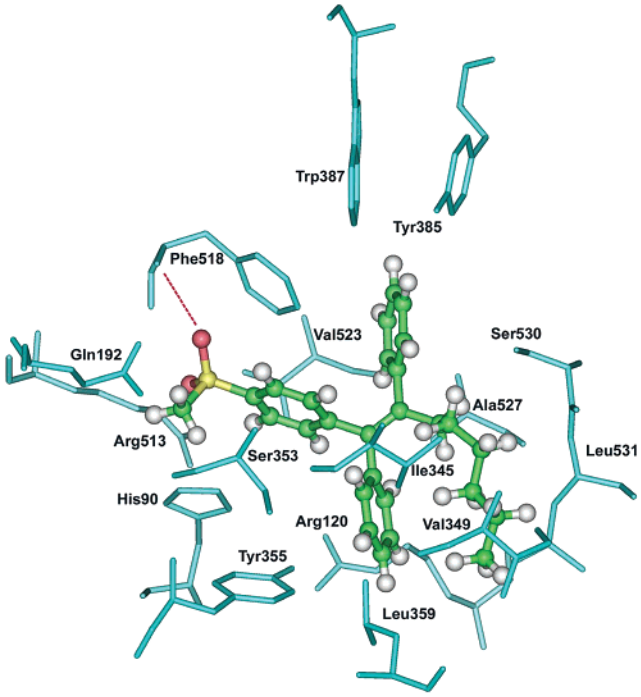


Figure 1. Molecular modeling (docking) of (*Z*)-**7d** in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

yielded compounds possessing good COX-2 inhibitory potency and selectivity.

The COX-1 and COX-2 inhibition studies of the 4-acetoxyphenyl compound (*Z*)-**10a** (R^1 = Et) showed that it is a potent (COX-2 IC_{50} = 0.05 μM; COX-1 IC_{50} = 0.25 μM), but moderately selective (SI = 5), COX-2 inhibitor (Table 1). It is noteworthy that (*Z*)-**10a** is a 60-fold more potent COX-2 inhibitor than the parent olefin (*Z*)-**7a** (R^1 = Et). Replacement of the ethyl substituent at the C-2 position by a *n*-butyl group [(*Z*)-**10b**, R^1 = *n*-butyl] increased COX-2 selectivity (COX-1 IC_{50} > 100 μM; COX-2 SI > 95) but decreased COX-2 potency (IC_{50} = 1.1 μM). Comparison of this *p*-OAc (*Z*)-olefin (**10b**) showed it is 9-fold more potent and 31-fold more selective than the parent (*Z*)-**7c** (R^1 = *n*-butyl) (Table 1).

Pharmacological studies were carried out to assess the in vivo antiinflammatory (AI) and analgesic activity of some of the most potent and selective COX-2 inhibitors [(*Z*)-**7a**, (*Z*)-**7d**, (*Z*)-**10a**] based on in vitro enzyme inhibition data (Table 1). In a carrageenan-induced rat paw edema assay, the 1,1,2-triarylbut-1-ene [(*Z*)-**7a**, ID_{50} = 1.9 mg/kg] and 1,1,2-triaryloct-1-ene [(*Z*)-**7d**, ID_{50} = 1.1 mg/kg] compounds having a C-2 phenyl substituent, and the but-1-ene having a C-2 4-acetoxyphenyl moiety [(*Z*)-**10a**, ID_{50} = 1.3 mg/kg] all exhibited superior AI activity relative to the reference drug celecoxib (ID_{50} = 10.8 mg/kg). In a rat model 4% NaCl-induced abdominal constriction assay, a 5 mg/kg po dose of (*Z*)-**7a**, (*Z*)-**7d**, or (*Z*)-**10a** exhibited good analgesic activities (43−63% range), that are comparable to celecoxib, at 30 or 60 min postdrug administration.

Conclusions

A new class of acyclic (*Z*)-2-alkyl-1,2-diphenyl-1-(4-methanesulfonylphenyl)ethenes have been designed. In vitro enzyme inhibition studies showed that COX-2 inhibitory potency and selectivity was dependent upon the alkyl substituent chain length at the C-2 position of the C=C bond. In this regard, the triaryl olefin **7d** [(*Z*)-1,2-diphenyl-1-(4-methanesulfonylphenyl)oct-1-ene, R^1 = *n*-hexyl] exhibited optimal COX-2 inhibitory potency (IC_{50} = 0.42 μM) and selectivity (COX-2 SI > 234). The structure−activity relationship data acquired show that appropriately substituted acyclic (*Z*)-olefins have the necessary geometry to provide potent and selective inhibition of the COX-2 isozyme, and that they exhibit excellent in vivo antiinflammatory and analgesic activities.

Experimental Section

General Procedure for the Synthesis of 1,2-Diphenyl-1-(4-methanesulfonylphenyl)alkyl-1-enes (7a−e). $TiCl_4$ (1.83 mL, 13 mmol) was added dropwise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL), under Ar at −10 °C, and after the addition was completed the reaction mixture was refluxed for 2 h. A solution of 4-methanesulfonylbenzophenone (**5**, 0.86 g, 3.3 mmol) and an alkanophenone (**6a**−**e**, 3.3 mmol) in THF (65 mL) were added to a cooled suspension of the titanium reagent at 0 °C, and the reaction mixture was refluxed for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (100 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material was removed by vacuum filtration through a pad of Celite 545. The organic

layer was separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic fractions were washed with water (10 mL), and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue from which the undesired homocoupled olefinic products were separated from the desired cross-coupled mixture of (*Z*)- and (*E*)-olefinic products (**7**) using *n*-hexanes−EtOAc (3:1, v/v) as eluant. Subsequent fractional recrystallizations (two or three) of this (*Z*):(*E*) mixture of olefins (**7**) from EtOH (95% w/v) afforded the respective (*Z*)-olefin product **7a**−**e**. The physical, spectroscopic, and microanalytical data for (*Z*)-**7a** is as follows: Yield, 62%; white crystals; mp 178−180 °C; IR (film): 1151, 1324 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.50 (q, 2H, J = 7.3 Hz, CH_2CH_3), 2.96 (s, 3H, SO_2CH_3), 7.05−7.42 (m, 12H, phenyl hydrogens and 4-methanesulfonylphenyl H-2, H-6), 7.56 (d, 2H, J = 8.2 Hz, 4-methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 13.4 (CH_2CH_3), 29.2 (CH_2CH_3), 44.4 (SO_2CH_3), 126.4, 126.8, 127.1, 128.1, 128.4, 129.4, 131.45 (C_{arom}-H), 137.0, 137.2, 141.0, 141.1, 145.0, 148.8 (C_{arom}-C; C_{olefin}-C; C_{arom}-S). Anal. ($C_{23}H_{22}O_2S \cdot 1/3H_2O$): C, H.

General Procedure for the Synthesis of (*Z*)-2-(4-Acetoxyphenyl)-1-(4-methanesulfonylphenyl)-1-phenylalkyl-1-enes (10a,b). $TiCl_4$ (1.83 mL, 13 mmol) was added dropwise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL) under an argon atmosphere at −10 °C, and this mixture was heated at reflux for 2 h to produce the titanium reagent. A cooled suspension of this titanium reagent was added to a solution of 4-methanesulfonylbenzophenone (**5**, 0.86 g, 3.3 mmol) and the respective 4-hydroxyalkanophenone (**8a**,**b**, 3.3 mmol) in THF (65 mL) at 0 °C, and the reaction was allowed to proceed at reflux for 2.5 h. After cooling to 25 °C, the reaction mixture was poured into a 10% aqueous K_2CO_3 solution (100 mL), this mixture was stirred vigorously for 5 min, and the dispersed insoluble material was removed by vacuum filtration through a Celite 545 pad. The organic fraction was separated, the aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic fractions were dried (Na_2SO_4). Removal of the solvent in vacuo afforded the respective 4-hydroxyphenyl olefinic intermediate (**9**, R^1 = Et, *n*-butyl), which was dissolved in ether (10 mL), and triethylamine (0.5 g, 5.0 mmol) was added. Acetyl chloride (0.39 g, 5.0 mmol) was added dropwise at 0 °C, and the reaction was allowed to proceed at 25 °C for 1.5 h with stirring prior to quenching with water (20 mL). The organic layer was separated, the aqueous layer was extracted with EtOAc (3 × 30 mL), the combined organic fractions were washed with water (10 mL), and the organic fraction was dried (Na_2SO_4). Removal of the solvent in vacuo gave a residue that was purified by silica gel flash column chromatography using *n*-hexanes−EtOAc (3:1, v/v) as eluant to afford the respective product (*Z*)-olefin product **10a**,**b**. The physical, spectroscopic and microanalytical data for (*Z*)-**10a** is as follows: Yield, 62%; white solid; mp 140−142 °C; IR (film): 1148, 1320 (SO_2), 1746 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.96 (t, 3H, J = 7.3 Hz, CH_2CH_3), 2.28 (s, 3H, $COCH_3$), 2.49 (q, 2H, J = 7.3 Hz, C=C−CH_2), 2.97 (s, 3H, SO_2CH_3), 6.78 (d, 2H, J = 8.2 Hz, 4-acetoxyphenyl H-3, H-5), 7.05−7.41(m, 9H, phenyl hydrogens, 4-methanesulfonylphenyl H-2, H-6 and 4-acetoxyphenyl H-2, H-6), 7.59 (d, 2H, J = 8.2 Hz, 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{25}H_{24}O_4S$): C, H.

Molecular Modeling (Docking) Study. Docking experiments were performed using Insight II software Version 2000.1 (Accelrys Inc.) running on a Silicon Graphics Octane 2 R14000A workstation according to a previously reported method.[4]

In Vitro Cyclooxygenase Inhibition Assays. The ability of the test compounds listed in the Table 1 to inhibit ovine COX-1 and COX-2 (IC_{50} values, μM) was determined using an enzyme immuno assay (EIA) kit (catalog number 560101, Cayman Chemical, Ann Arbor, MI) according to our previously reported method.[13]

Antiinflammatory Assay. Antiinflammatory activity was measured using a carrageenan-induced rat paw edema assay according to a previously reported procedure.[14]

Analgesic Assay. Analgesic activity was determined using a 4% sodium chloride-induced writhing (abdominal constriction) assay previously reported.[15]

Acknowledgment. We are grateful to (i) the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research, and (ii) the Alberta Heritage Foundation for Medical Research (AHFMR) for a postdoctoral fellowship award (to M. J. U.), and a graduate scholarship (to P. R.).

Supporting Information Available: Structures for compounds **1**−**4** (Chart 1), spectroscopic data (IR, ^1H NMR, ^{13}C NMR) for the (*Z*)-olefins **7b**−**e** (Scheme 1) and **10b** (Scheme 2), the X-ray crystal data for compound (*Z*)-**7a**, and microanalytical data are available free of charge on the Internet at http://pubs.acs.org.

References

(1) Silverstein, F. E.; Faich, G.; Goldstein, J. L.; Simon, L. S.; Pincus, T.; Whelton, A.; Makuch, R.; Eisen, G.; Agrawal, N. M.; Stenson, W. F.; Burr, A. M.; Zhao, W. W.; Kent, J. D.; Lefkowith, J. B.; Verburg, K. M.; Geis, G. S. Gastrointestinal toxicity with celecoxib vs nonsteroidal antiinflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. *JAMA* **2000**, *284*, 1247−1255.

(2) Bombardier, C.; Laine, L.; Reicin, A.; Shapiro, D.; Burgos-Vargas, R.; Davis, B.; Day, R.; Ferraz, M. B.; Hawkey, C. J.; Hochberg, M. C.; Kvien, T. K.; Schnitzer, T. J. Group comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N. Engl. J. Med.* **2000**, *343*, 1520−1528.

(3) Atkinson, J. G.; Wang, Z. Stilbene derivatives useful as cyclooxygenase-2 inhibitors. World Patent WO 96/13483, 9th May, **1996**; *Chem. Abstr. 125*, 114294.

(4) Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. Design of acyclic triaryl olefins: a new class of potent and selective cyclooxygenase-2 (COX-2) inhibitors. *Bioorg. Med. Chem. Lett*. **2004**, *14*, 1953−1956.

(5) McCague, R.; Leclercq, G.; Legros, N.; Goodman, J.; Blackburn, G. M.; Jarman, M.; Foster, A. B. Derivatives of tamoxifen. Dependence of antiestrogenicity on the 4-substituent. *J. Med. Chem.* **1989**, *32*, 2527−2533.

(6) Balfe, M. P.; Dabby, R. E.; Kenyon, J. Alkyl oxygen fission in carboxylic esters. Part VIII. Esters of *p*-methylthio and *p*-methanesulfonyldiphenylcarbinols. *J. Chem. Soc.* **1951**, 382−385.

(7) Detsi, A.; Koufaki, M.; Calogeropoulou. Synthesis of (*Z*)-4-hydroxytamoxifen and (*Z*)-2-[4-[1-(*p*-hydroxyphenyl)-2-phenyl]-1-butenyl]phenoxyacetic acid. *J. Org. Chem*. **2002**, *67*, 4608−4611.

(8) Coe, P. L.; Scriven, C. E. Crossed coupling of functionalized ketones by low valent titanium (the McMurry reaction): a new stereoselective synthesis of tamoxifen. *J. Chem. Soc., Perkin Trans. 1* **1986**, 475−477.

(9) Uddin, M. J.; Rao, P. N. P.; Knaus, E. E. Methylsulfonyl and hydroxyl substituents induce (*Z*)-stereocontrol in the McMurry olefination reaction. *Synlett* **2004**, 1513−1516.

(10) Rahim, M. A.; Praveen Rao, P. N.; Knaus, E. E. Isomeric acetoxy analogues of rofecoxib: A novel class of highly potent and selective cyclooxygenase-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2753−2756.

(11) McMurry, J. E. Carbonyl-coupling reactions using low-valent titanium. *Chem. Rev.* **1989**, *89*, 1513−1524.

(12) McMurry, J. E.; Fleming, M. P.; Kees, K. L.; Krepski, L. R. Titanium-induced reductive coupling of carbonyls to olefins. *J. Org. Chem.* **1978**, *43*, 3255−3266.

(13) Rao, P. N. Praveen; Amini, Mohsen; Li, Huiying; Habeeb, Amgad G.; Knaus, Edward E. Design, synthesis, and biological evaluation of 6-substituted-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-ones: A novel class of diarylheterocyclic selective cyclooxygenase-2 inhibitors. *J. Med. Chem.* **2003**, *46*, 4872−4882.

(14) Winter, C. A.; Risley, E. A.; Nuss, G. W.; Carrageenan-induced edema in hind paw of the rat as an assay for antiinflammatory drugs. *Proc. Soc. Exp. Biol. Med*. **1962**, *111*, 544−552.

(15) Fukawa, K.; Kawano, O.; Hibi, M.; Misaka, N.; Ohba, S.; Hatanaka, Y. Method for evaluating analgesic agents in rats. *J. Pharmacol. Methods* **1980**, *4*, 251−259.

JM049523Y