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Bioorganic & Medicinal Chemistry 13 (2005) 417–424
Bioorganic & Medicinal Chemistry

Design and synthesis of (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-enes and (*Z*)-1-(4-azidophenyl)-1,2-diphenylalk-1-enes: novel inhibitors of cyclooxygenase-2 (COX-2) with anti-inflammatory and analgesic activity

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Received 6 September 2004; revised 6 October 2004; accepted 6 October 2004
Available online 28 October 2004

Abstract—A group of novel (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-enes was designed for evaluation as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1/COX-2 enzyme inhibition studies identified (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)oct-1-ene (**8d**) as a highly potent (IC_{50} = 0.03 μM), and an extremely selective [COX-2 SI (selectivity index) > 3,333], COX-2 inhibitor that showed good anti-inflammatory (AI) activity (ID_{50} = 2.8 mg/kg). A molecular modeling (docking) study showed that the *p*-$MeSO_2NH$ group present in (*Z*)-**8d** inserts deep inside the 2°-pocket of the COX-2 binding site, it undergoes a hydrophobic interaction with Ala^{516} and Gly^{519}, and one of the *O*-atoms of the $MeSO_2$ group participates in a weak hydrogen bonding interaction with the NH_2 of Arg^{513} (distance = 3.85 Å). Similar in vitro COX-1/COX-2 enzyme inhibition studies showed that the azido compound 1-(4-azidophenyl)-1,2-diphenyloct-1-ene (**9c**) is also a potent and selective COX-2 inhibitor (COX-2 IC_{50} = 0.11 μM: SI > 909) that exhibits good AI activity (ID_{50} = 5.0 mg/kg). A docking experiment to determine the orientation of (*Z*)-**9c** within the COX-2 binding site showed that the linear *p*-N_3 group inserts into the COX-2 2°-pocket, where it undergoes an ion–ion (electrostatic) interaction with Arg^{513}. Structure–activity data acquired indicate that an olefin having either a C-1 *p*-$MeSO_2NH$–phenyl, or a *p*-N_3–phenyl, substituent, that is, *cis* to a C-2 unsubstituted phenyl substituent, in conjunction with C-1 unsubstituted phenyl and C-2 alkyl substituents, provides a novel template to design acyclic olefinic COX-2 inhibitors.

1. Introduction

Prostaglandins are important biological mediators of inflammation, originating from the biotransformation of arachidonic acid catalyzed by cyclooxygenase (COX).[1] A selective cyclooxygenase-2 (COX-2) inhibitor allows the desired synthesis of cytoprotective prostaglandins, in conjunction with a simultaneous inhibition of proinflammatory prostaglandin synthesis, thereby reducing dyspepsia and ulceration.[2] The discovery of selective COX-2 inhibitors, such as celecoxib (**1**),[3] rofecoxib (**2**) which was recently withdrawn from the market due to its adverse cardiovascular effects, and valdecoxib (**3**) was made possible based on insights into the properties of the COX-1 and COX-2 binding sites acquired from X-ray crystal structure data.[4,5] Recently, we designed a novel class of acyclic 2-alkyl-1,1,2-triaryl (*Z*)-olefins (**4**), possessing a *p*-$MeSO_2$ group on the C-1 phenyl ring, that exhibited selective COX-2 inhibitory activity (Fig. 1).[6] As a part of our ongoing program to design novel selective COX-2 inhibitors, we describe herein the synthesis and biological evaluation of a novel group of 2-alkyl-1,1,2-triaryl (*Z*)-olefins having either a *p*-$MeSO_2NH$ or a *p*-N_3 COX-2 pharmacophore on the C-1 phenyl ring.

2. Chemistry

The anilino olefinic intermediates **7** (R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl) were generated in situ using a McMurry olefination reaction that involved the Zn–$TiCl_4$ catalyzed reductive cross-coupling of 4-aminobenzophenone (**5**) and an alkanophenone **6**

Keywords: Cyclooxygenase-2 (COX-2); Triaryl (*Z*)-olefins; Methanesulfonamide; Azide.
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doi:10.1016/j.bmc.2004.10.017

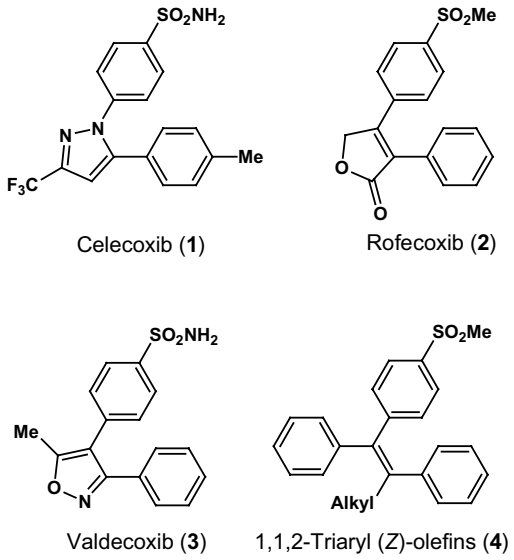
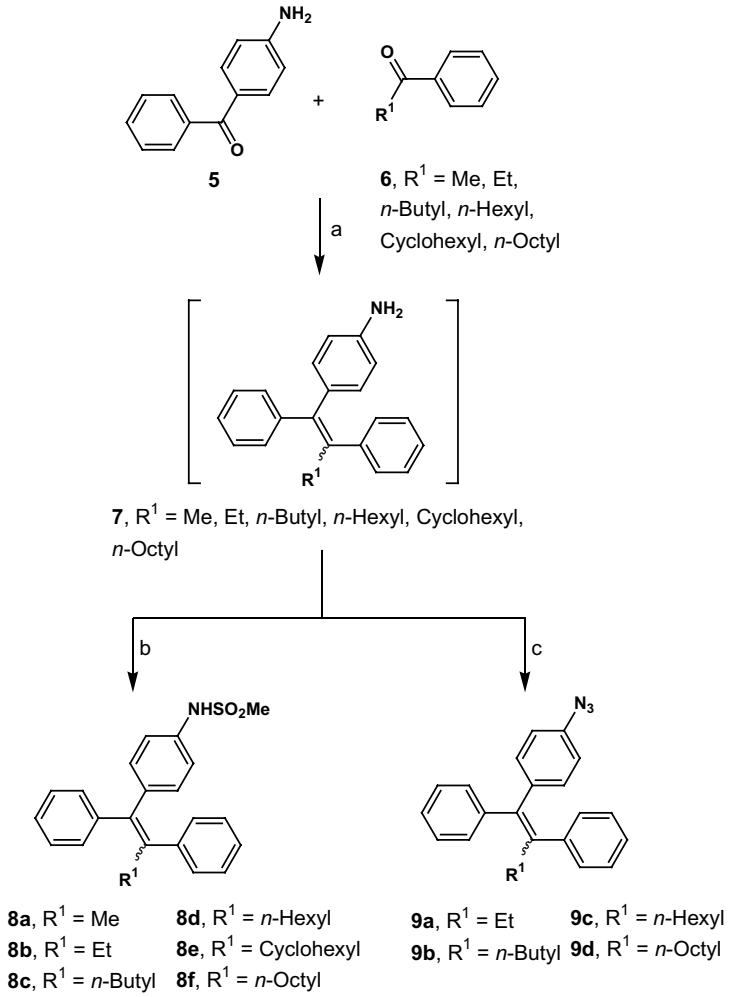


Figure 1. Representative cyclooxygenase-2 (COX-2) inhibitors.

(R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl). These reactions proceed with predominant (*Z*)-selectivity that was determined after conversion to either the respective olefinic sulfonamide **8a**–**f** (R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl), or azide **9a**–**d** (R^1 = Et, *n*-butyl, *n*-hexyl, *n*-octyl) (**9b**, *E:Z* ratio 1:9.2), product.[6] The undesired homo-coupled olefinic products formed in this reaction were separated from the desired cross-coupled mixture of (*Z*)- and (*E*)-olefins **8a**–**f** or **9a**–**d** by silica gel column chromatography. Subsequent consecutive recrystallizations to isolate the predominant (*Z*)-olefin from the (*Z*):(*E*) olefinic mixture provided the respective target (*Z*)-olefins **8a**–**f** in 60–65%, or **9a**–**d** in 51–56%, isolated yields (Scheme 1). The structures of the (*Z*)-olefin products **8a**–**f** and **9a**–**d** were consistent with respective spectral and microanalytical data. In addition, the absolute stereochemistry of (***Z***)-**8a** (R^1 = Me) was established unambiguously from the single crystal X-ray analysis (Fig. 2).[7] It has been proposed that a titanium-induced McMurry olefination reaction proceeds via deoxygenation of the bidentate pinacolic intermediate that is formed by homolytic coupling of two radical anion species generated from reduction of carbonyl compounds.[8] Although the mechanism of this (*Z*)-selective McMurry reaction is still unclear, a preferred orientation due to a weak interaction between



Scheme 1. Reagents and conditions: (a) Zn, $TiCl_4$, THF, reflux 4.5 h; (b) $MeSO_2Cl$, TEA, CH_2Cl_2, 25 °C, 15 h; (c) $NaNO_2$/HCl, NaN_3, 0–5 °C, 1 h.

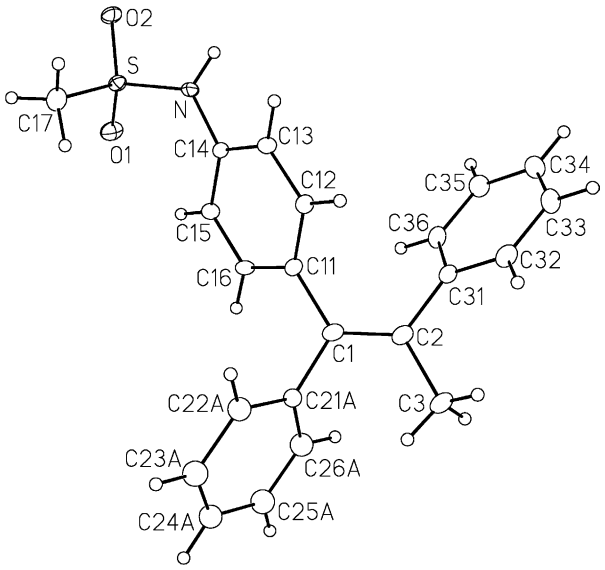


Figure 2. X-ray crystal structure of (*Z*)-**8a**.

the anilino ring of ketone **5** and the phenyl ring of ketone **6** appears to be an important factor that affects the (*Z*)-stereocontrol of the olefination reaction by orienting these two phenyl rings *cis* to each other in the transition state.[9]

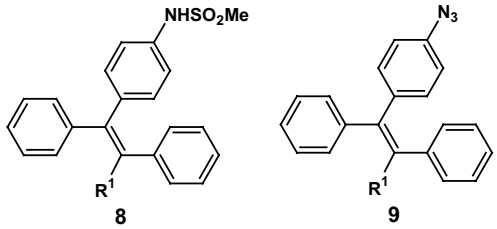
3. Results and discussion

Recently, we reported that triaryl (*Z*)-olefins having a $MeSO_2$ COX-2 pharmacophore positioned at the *para*-position of either a C-1 or a C-2 phenyl ring, where the length of the C-2 alkyl substituent was varied, exhibit selective COX-2 inhibition. Structure–activity studies showed that (*Z*)-1,2-diphenyl-1-(4-methylsulfonylphenyl)oct-1-ene exhibited maximal in vivo anti-inflammatory activity (ID_{50} 1.1 mg/kg).[6] The structurally related 1,1-diphenyl-2-(4-methylsulfonylphenyl)hex-1-ene was identified as a potent COX-2 inhibitor (IC_{50} = 0.014 μM) with an extremely high COX-2 SI (selectivity index) > 7,142.[10] These studies have now been extended to include the design of 2-alkyl-1,1,2-triaryl (*Z*)-olefins possessing either a *p*-$MeSO_2NH$ or a *p*-N_3 substituent on the C-1 phenyl ring. Accordingly, in vitro COX-1/COX-2 enzyme inhibition studies showed that the *p*-$MeSO_2NH$ compound (*Z*)-**8a** (R^1 = Me) is a moderately selective inhibitor of COX-2 (COX-1 IC_{50} > 100 μM; COX-2 IC_{50} = 33.1 μM; SI > 3). Further inhibition studies showed that COX-2 inhibitory potency and selectivity increased moderately for (*Z*)-**8b** (R^1 = Et) (COX-2 IC_{50} = 1.8 μM: SI = 17), and considerably for (*Z*)-**8c** (R^1 = *n*-butyl) (COX-2 IC_{50} = 0.32 μM; SI > 312). A further increase in alkyl chain length resulted in a dramatic increase in both COX-2 inhibitory potency (IC_{50} = 0.03 μM) and selectivity (SI > 3,333). In this regard, (*Z*)-**8d** (R^1 = *n*-hexyl) was a 2.4-fold more potent, and a 7-fold more selective, COX-2 inhibitor than celecoxib, and a 17-fold more potent COX-2 inhibitor than rofecoxib. The cyclohexyl compound (*Z*)-**8e**, obtained by replacement of the *n*-hexyl chain of (*Z*)-**8d** with a cyclohexyl ring, was an inactive inhibitor of the COX-1 and COX-2 isozymes (IC_{50} > 100 μM). A further increase in alkyl chain length provided (*Z*)-**8f** (R^1 = *n*-octyl) that showed decreased COX-2 inhibitory potency and selectivity (COX-1 IC_{50} = 30.5 μM; COX-2 IC_{50} = 6.0 μM) (Table 1).

A molecular modeling (docking) simulation was performed to investigate the binding interaction of the most potent and selective COX-2 inhibitor (*Z*)-**8d** within the COX-2 binding site (Fig. 3). The C-1 *p*-$MeSO_2NH$–phenyl ring of (*Z*)-**8d** is oriented toward the COX-2 2°-pocket. As expected, the $MeSO_2NH$ COX-2 pharmacophore was in close contact with amino acid residues Val^{523}, Phe^{518}, Ala^{516}, Arg^{513}, Gln^{192}, and His^{90} lining the COX-2 binding site. The methyl group of the $MeSO_2NH$ moiety is involved in a hydrophobic binding interaction with Ala^{516} and Gly^{519}, whereas one of the *O*-atoms of the $MeSO_2$ moiety forms a weak hydrogen bonding interaction with the N*H*$_2$ of Arg^{513} (distance = 3.85 Å). The distance between the N*H* of $MeSO_2NH$ and *N*H$_2$ of Gln^{192} is about 4.90 Å. In addition, the distance between the N*H* of $MeSO_2NH$ and N^3 of His^{90} at the entrance to the COX-2 2°-pocket is about 4.49 Å. The unsubstituted C-2 phenyl ring that is *cis* to the C-1 *p*-$MeSO_2NH$–phenyl substituent is oriented toward a hydrophobic cavity at the apex of the binding site (Leu^{384}, Tyr^{385}, and Trp^{387}) with an interspatial distance of about 4.49 Å from the *O*H of Tyr^{385}. The central C=C is located in a area surrounded by Gly^{526} and Ala^{527}, whereas 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 closer to Tyr^{355} and Arg^{120}. The C-2 *n*-hexyl chain is localized in a hydrophobic area closer to the mouth of the COX-2 binding site, where it interacts with Ser^{530}, Leu^{531}, Val^{349}, Ile^{345}, Leu^{359}, and Leu^{117} (distance < 5 Å).

It was demonstrated previously that 3,4,6-triphenylpyran-2-ones having a dipolar *p*-N_3 group on the C-3 phenyl ring is a selective COX-2 inhibitor, which undergoes an electrostatic (ion–ion) interaction with Arg^{513} in the COX-2 2°-pocket.[11] It was therefore of interest to synthesize *p*-N_3 derivatives of 2-alkyl-1,1,2-triaryl (*Z*)-olefins for biologically evaluation. Accordingly, the in vitro COX-1/COX-2 enzyme inhibition data showed that the *p*-N_3 compound (*Z*)-**9a** (R^1 = Et) is a selective inhibitor of COX-2 (COX-1 IC_{50} > 100 μM; COX-2 IC_{50} = 0.28 μM; SI > 357). When the alkyl chain length was increased, COX-2 inhibitory potency decreased as indicated by (*Z*)-**9b** (R^1 = *n*-butyl; COX-2 IC_{50} = 1.0 μM). (*Z*)-**9c** (R^1 = *n*-hexyl) exhibited an optimal combination of COX-2 inhibitory potency (COX-2 IC_{50} = 0.11 μM) and selectivity (SI > 909), being four-fold more potent and four-fold more selective than rofecoxib. A further increase in alkyl chain length provided (*Z*)-**9d** (R^1 = *n*-octyl) having a dramatically increased COX-2 potency (COX-2 IC_{50} = 0.014 μM), but much lower COX-2 selectivity (SI = 15) (Table 1). A molecular modeling study, where (*Z*)-**9c** (R^1 = *n*-hexyl) was docked in the COX-2 binding site, showed that

Table 1. In vitro COX-1/COX-2 enzyme inhibition data for (*Z*)-olefins **8a–f**, **9a–d**, and in vivo anti-inflammatory and analgesic activity data for (*Z*)-olefins **8a–d** and **9c**



Compd	R^1	COX-1	COX-2	COX-2	AI activity[c]	Analgesic activity[d]	
		IC_{50} (μM)[a]	IC_{50} (μM)[a]	SI[b]	ID_{50} (mg/kg)	% Inhibition (30 min)	% Inhibition (60 min)
(*Z*)-8a	Me	>100	33.1	>3	2.1	41.6 ± 8.3	58.3 ± 8.3
(*Z*)-8b	Et	31	1.8	17	2.5	62.5 ± 14.4	55.2 ± 7.2
(*Z*)-8c	*n*-Butyl	>100	0.32	>312	1.8	60.0 ± 8.1	55.0 ± 12.2
(*Z*)-8d	*n*-Hexyl	>100	0.03	>3333	2.8	56.1 ± 12.8	44.1 ± 9.6
(*Z*)-8e	Cyclohexyl	>100	>100	—	—	—	—
(*Z*)-8f	*n*-Octyl	30.5	6.0	5	—	—	—
(*Z*)-9a	Et	>100	0.28	>357	—	—	—
(*Z*)-9b	*n*-Butyl	>100	1.0	>100	—	—	—
(*Z*)-9c	*n*-Hexyl	>100	0.11	>909	5.0	61.1 ± 9.3	41.6 ± 5.5
(*Z*)-9d	*n*-Octyl	0.21	0.014	15	—	—	—
Celecoxib	—	33.1	0.07	472	10.8	69.3 ± 12.1[e]	79.5 ± 2.0[e]
Rofecoxib	—	>100	0.50	>200	—	—	—

[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.

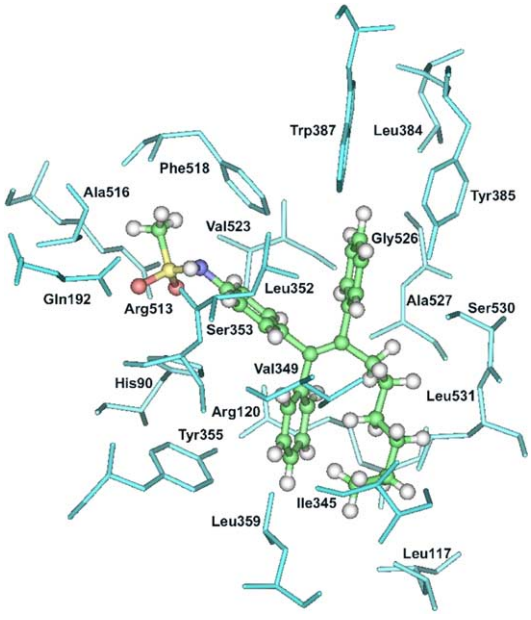


Figure 3. Docking of (*Z*)-**8d** in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

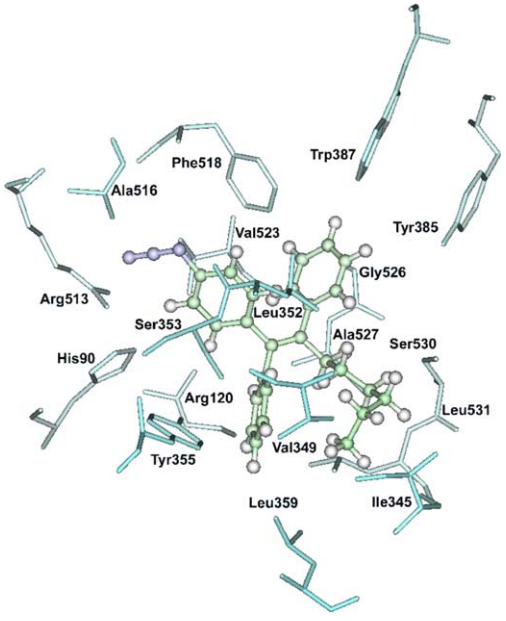


Figure 4. Docking of (*Z*)-**9c** in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues have been removed to improve clarity.

the C-1 *p*-azido-phenyl ring is surrounded by Val^{523}, Ser^{353}, and Phe^{518} (Fig. 4). The *p*-azido substituent is oriented in the vicinity of the 2°-pocket of COX-2 (Phe^{518}, Arg^{513}, Ala^{516}, and Gln^{192}). It is known that

replacement of His^{513} in COX-1 by Arg^{513} in COX-2 plays a key role in the hydrogen-bond network of the COX-2 binding site.[12] Accordingly, the linear dipolar azido substituent present in (*Z*)-**9c** is involved in an ion–ion (electrostatic) interaction with Arg^{513}. The distance between the terminal *N*-atom of the azido substituent and the N*H*$_2$ of Arg^{513} is about 3.64 Å, whereas the distance between the terminal *N*-atom of the azido substituent and the N*H* of His^{90} is about 4.13 Å. Similar to (*Z*)-**8d**, the C=C of (*Z*)-**9c** is in close contact with Gly^{526} and Ala^{527}, whereas the C-2 unsubstituted phenyl ring *cis* to the C-1 *p*-N_3–phenyl substituent is oriented toward Leu^{384}, Tyr^{385}, and Trp^{387} at the top of the COX-2 binding site. Unlike (*Z*)-**9c**, the C-2 phenyl ring of (*Z*)-**8d** is further removed from Tyr^{385} (distance = 6.31 Å). The C-1 unsubstituted phenyl ring in (*Z*)-**9c**, that is *cis* to the C-2 *n*-hexyl substituent, is positioned closer to the mouth of the COX-2 binding site such that the distance between the center of the phenyl ring and the O*H* of Tyr^{355} is about 4.9 Å. Similar to (*Z*)-**8d**, the C-2 *n*-hexyl chain present in (*Z*)-**9c** is oriented toward a hydrophobic region closer to the mouth of the COX-2 binding site where it interacts with Ser^{530}, Leu^{531}, Val^{349}, Ile^{345}, and Leu^{359} (distance ≈ 5 Å). It is interesting to note that the terminal methyl group of the *n*-hexyl substituent is further removed from Leu^{117} (distance = 7.5 Å) compared to (*Z*)-**8d** (distance < 5 Å), which could provide a plausible explanation for the greater COX-2 inhibitory potency and selectivity exhibited by (*Z*)-**8d** in comparison with (*Z*)-**9c**.

Pharmacological studies were carried out to examine the in vivo anti-inflammatory (AI) and analgesic activity of some of the most potent and selective COX-2 inhibitors [(*Z*)-**8a**, (*Z*)-**8b**, (*Z*)-**8c**, (*Z*)-**8d**, and (*Z*)-**9c**] based on in vitro enzyme inhibition data (Table 1). In a carrageenan-induced rat paw edema assay model, the olefins (*Z*)-**8a** (R^1 = Me) (ID_{50} = 2.1 mg/kg), (**Z**)-**8b** (R^1 = Et) (ID_{50} = 2.5 mg/kg), (*Z*)-**8c** (R^1 = *n*-butyl) (ID_{50} = 1.8 mg/kg), (*Z*)-**8d** (R^1 = *n*-hexyl) (ID_{50} = 2.8 mg/kg), and (*Z*)-**9c** (R^1 = *n*-hexyl) (ID_{50} = 5.0 mg/kg) 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 (analgesic) assay, a 5 mg/kg po dose of (*Z*)-**8a**, (*Z*)-**8b**, (*Z*)-**8c**, (*Z*)-**8d**, and (*Z*)-**9c** exhibited good analgesic activities (41–62% range) at 30 or 60 min post drug administration.

4. Conclusions

A novel group of (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-enes was designed, synthesized and biologically evaluated as selective cyclooxygenase-2 (COX-2) inhibitors. In vitro COX-1/COX-2 enzyme inhibition studies identified (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)oct-1-ene (**8d**) as a highly potent (IC_{50} = 0.03 μM), and an extremely selective (SI > 3,333) COX-2 inhibitor that showed excellent anti-inflammatory activity (ID_{50} = 2.8 mg/kg). A molecular modeling (docking) study showed that one of the *O*-atoms of the *p*-$MeSO_2NH$ group forms a hydrogen bond with the N*H*$_2$ of Arg^{513} (distance = 3.85 Å) in the COX-2 2°-pocket. It was also discovered that the azido compound 1-(4-azidophenyl)-1,2-diphenyloct-1-ene (**9c**) is a potent and selective COX-2 inhibitor (COX-2 IC_{50} = 0.11 μM; SI > 909) that elicits good anti-inflammatory activity (ID_{50} = 5.0 mg/kg). Docking (*Z*)-**9c** in the COX-2 binding site showed that the *p*-N_3 substituent undergoes an ion–ion (electrostatic) interaction with Arg^{513} in the COX-2 2°-pocket. Structure–activity data acquired in this investigation shows that an olefin possessing (i) the absolute (*Z*)-stereochemistry, (ii) a *p*-$MeSO_2NH$–phenyl or *p*-N_3–phenyl moiety 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, constitutes a useful template to design acyclic triaryl olefinic COX-2 inhibitors.

5. Experimental

Melting points were determined using a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded as films on NaCl plates using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer, where *J* (coupling constant) values are estimated in Hz. ^{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 quaternary carbon resonances appear as negative peaks. Elemental analysis (EA) were performed for C, H (Micro-analytical Service Laboratory, Department of Chemistry, University of Alberta). X-ray crystal data were acquired on a Brucker PLATFORM/SMART 1000 CCD diffractometer (X-ray Crystallography Laboratory, Department of Chemistry, University of Alberta). Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70–230 mesh). All other reagents, purchased from the Aldrich Chemical Company (Milwaukee, WI), were used without further purification. Male Sprague–Dawley rats, used in the anti-inflammatory and analgesic screens, were purchased from Animal Health Services at the University of Alberta, and experiments were carried out using protocols approved by the Animal Welfare Committee, University of Alberta.

5.1. General procedure for the synthesis of 1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-enes (8a–f)

$TiCl_4$ (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-aminobenzophenone (**5**, 0.65 g, 3.3 mmol) and an alkanophenone (**6a–f**, R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl, 3.3 mmol) in THF (65 mL) was 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 onto 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 afforded the respective 4-aminophenyl olefinic intermediate **7a–f** (R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl), which was dissolved in CH_2Cl_2 (20 mL) and triethylamine (0.5 g, 5.0 mmol) was added. Methanesulfonyl chloride (0.42 g, 3.7 mmol) was added dropwise at 0 °C, and the reaction was allowed to proceed for 15 h at 25 °C with stirring. Water (15 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL), and the combined organic fractions were washed with water (3×30 mL). The organic fraction was dried (Na_2SO_4) and the solvent was removed in vacuo to give a residue. The undesired homo-coupled olefinic product was separated from the desired cross-coupled mixture of (*E*)- and (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-ene (**8a–f**) by silica gel column chromatography using *n*-hexane–EtOAc (3:1, v/v) as eluant. Subsequent fractional recrystallizations (one or two) of each (*Z*):(*E*) mixture from EtOH (95% w/v) afforded the respective (*Z*)-1,2-diphenyl-1-(4-methanesulfonamidophenyl)alk-1-ene **8a–f** (R^1 = Me, Et, *n*-butyl, *n*-hexyl, cyclohexyl, *n*-octyl). The physical, spectroscopic, and microanalytical data for the (*Z*)-olefins **8a–f** are listed below.

5.2. (*Z*)-1,2-Diphenyl-1-(4-methanesulfonamidophenyl)-prop-1-ene (8a)

Yield, 60%; pale brown crystals; mp 198–200 °C; IR (film): 1143, 1327 (SO_2), 3228 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13 (s, 3H, CH_3), 2.91 (s, 3H, SO_2CH_3), 6.27 (br s, 1H, N*H*), 6.84–6.90 (m, 4H, 4-methanesulfonamidophenyl hydrogens), 7.09–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{22}H_{21}NO_2S{\cdot}1/6H_2O$: C, 72.09; H, 5.82; N, 3.82. Found: C, 72.09; H, 5.67; N, 3.68.

5.3. (*Z*)-1,2-Diphenyl-1-(4-methanesulfonamidophenyl)-but-1-ene (8b)

Yield, 63%; pale yellow crystals; mp 214–216 °C; IR (film): 1150, 1322 (SO_2), 3235 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.93 (t, 3H, $J = 7.3$ Hz, CH_2CH_3), 2.47 (q, 2H, $J = 7.3$ Hz, C=C–CH_2), 2.90 (s, 3H, SO_2CH_3), 6.12 (br s, 1H, N*H*), 6.82–6.91 (m, 4H, 4-methanesulfonamidophenyl hydrogens), 7.08–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{23}H_{23}NO_2S$: C, 73.18; H, 6.14; N, 3.71. Found: C, 72.82; H, 6.30; N, 3.57.

5.4. (*Z*)-1,2-Diphenyl-1-(4-methanesulfonamidophenyl)-hex-1-ene (8c)

Yield, 64%; pale yellow crystals; mp 186–188 °C; IR (film): 1134, 1324 (SO_2), 3215 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (t, 3H, $J = 6.9$ Hz, CH_2CH_3), 1.18–1.33 [m, 4H, $(CH_2)_2CH_3$], 2.42 (t, 2H, $J = 7.3$ Hz, C=C–CH_2), 2.90 (s, 3H, SO_2CH_3), 6.12 (br s, 1H, N*H*), 6.82–6.88 (m, 4H, 4-methanesulfonamidophenyl hydrogens), 7.07–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{25}H_{27}NO_2S$: C, 74.04; H, 6.71; N, 3.45. Found: C, 73.97; H, 6.70; N, 3.63.

5.5. (*Z*)-1,2-Diphenyl-1-(4-methanesulfonamidophenyl)-oct-1-ene (8d)

Yield, 62%; pale yellow crystals; mp 174–176 °C; IR (film): 1155, 1320 (SO_2), 3237 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J = 7.3$ Hz, CH_2CH_3), 1.10–1.33 [m, 8H, $(CH_2)_4CH_3$], 2.41 (t, 2H, $J = 7.9$ Hz, C=C–CH_2), 2.90 (s, 3H, SO_2CH_3), 6.12 (br s, 1H, N*H*), 6.82–6.88 (m, 4H, 4-methanesulfonamidophenyl hydrogens), 7.07–7.39 (m, 10H, phenyl hydrogens); ^{13}C NMR (75 MHz; $CDCl_3$): δ 14.0 (CH_3), 22.5, 28.7, 29.3, 31.3, 35.8 (CH_2), 39.1 (SO_2CH_3), 119.6, 126.2, 126.6, 127.7, 128.1, 129.3, 129.4, 131.8 (C_{arom}–H), 133.9, 137.8, 140.3, 141.7, 142.1, 142.9 (C_{arom}–N, C_{olefin}–C, C_{arom}–C); Anal. Calcd for $C_{27}H_{31}NO_2S$: C, 74.79; H, 7.21; N, 3.23. Found: C, 74.76; H, 6.86; N, 3.14.

5.6. (*Z*)-2-Cyclohexyl-1,2-diphenyl-1-(4-methanesulfonamidophenyl)ethene (8e)

Yield, 60%; brown crystals; mp 194–196 °C; IR (film): 1125, 1318 (SO_2), 3210 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.88–1.70 [m, 10H, $(CH_2)_5$], 2.55–2.65 (m, 1H, C=C–C*H*), 2.82 (s, 3H, SO_2CH_3), 6.11 (br s, 1H, N*H*), 6.77 (d, 2H, $J = 8.2$ Hz, 4-methanesulfonamidophenyl H-3, H-5), 6.88 (d, 2H, $J = 8.2$ Hz, 4-methanesulfonamidophenyl H-2, H-6), 7.01–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{27}H_{29}NO_2S$: C, 75.14; H, 6.77; N, 3.25. Found: C, 74.90; H, 6.65; N, 3.19.

5.7. (*Z*)-1,2-Diphenyl-1-(4-methanesulfonamidophenyl)-dec-1-ene (8f)

Yield, 65%; pale yellow crystals; mp 164–166 °C; IR (film): 1155, 1320 (SO_2), 3223 (NH) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85 (t, 3H, $J = 7.3$ Hz, CH_2CH_3), 1.16–1.57 [m, 12H, $(CH_2)_6CH_3$], 2.41 (t, 2H, $J = 7.6$ Hz, C=C–CH_2), 2.90 (s, 3H, SO_2CH_3), 6.16 (br s, 1H, N*H*), 6.82-6.85 (m, 4H, 4-methanesulfonamidophenyl hydrogens), 7.07–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{29}H_{35}NO_2S$: C, 75.45; H, 7.64; N, 3.03. Found: C, 75.03; H, 7.79; N, 2.89.

5.8. General procedure for the synthesis of (*Z*)-1-(4-azidophenyl)-1,2-diphenylalk-1-enes (9a–d)

$TiCl_4$ (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-aminobenzophenone (**5**, 0.65 g, 3.3 mmol) and an alkanophenone (**6a–d**, R^1 = Et, *n*-butyl, *n*-hexyl, *n*-octyl, 3.3 mmol) in THF (65 mL) was 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 onto 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 fil-

tration 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 the respective 4-aminophenyl olefinic intermediate **7a–d** (R^1 = Et, *n*-butyl, *n*-hexyl, *n*-octyl), which was dissolved in HCl (37% w/v, 20 mL). A solution of $NaNO_2$ (0.24 g, 3.37 mmol) in H_2O (27 mL) was added dropwise at 0–5 °C during 15 min. A solution of NaN_3 (2.14 g, 33 mmol) in H_2O (8 mL) was added dropwise at 0–5 °C over a period of 15 min and the reaction was allowed to proceed for 30 min at 25 °C. The reaction mixture was extracted with EtOAc (3 × 50 mL), the combined organic fractions were dried (Na_2SO_4), and the solvent was removed in vacuo to give a residue. The undesired homo-coupled olefinic product was separated from the desired cross-coupled mixture of (*E*)- and (*Z*)-1-(4-azidophenyl)-1,2-diphenylalk-1-ene **(9a–d)** by silica gel column chromatography using *n*-hexane–EtOAc (3:1, v/v) as eluant. Subsequent recrystallizations (two or three) of each (*Z*):(*E*) mixture from petroleum ether afforded the respective (*Z*)-1-(4-azidophenyl)-1,2-diphenylalk-1-ene **9a–d** (R^1 = Et, *n*-butyl, *n*-hexyl, *n*-octyl). The physical, spectroscopic and microanalytical data for the (*Z*)-olefins **9a–d** are listed below.

5.9. (*Z*)-1-(4-Azidophenyl)-1,2-diphenylbut-1-ene (9a)

Yield, 52%; brown needles; mp 99–101 °C; IR (film): 2126 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H, J = 7.0 Hz, CH_2CH_3), 2.48 (q, 2H, J = 7.0 Hz, C≡C–CH_2), 6.68 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-3, H-5), 6.86 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-2, H-6), 7.00–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{22}H_{19}N_3$: C, 81.20; H, 5.89; N, 12.91. Found: C, 81.26; H, 6.01; N, 12.94.

5.10. (*Z*)-1-(4-Azidophenyl)-1,2-diphenylhex-1-ene (9b)

Yield, 51%; brown crystals; mp 88–90 °C; IR (film): 2117 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.78 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.19–1.40 [m, 4H, $(CH_2)_2$], 2.42 (t, 2H, J = 7.0 Hz, C≡C–CH_2), 6.67 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-3, H-5), 6.85 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-2, H-6), 7.00–7.41 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{24}H_{23}N_3$: C, 81.55; H, 6.56; N, 11.89. Found: C, 81.57; H, 6.64; N, 11.92.

5.11. (*Z*)-1-(4-Azidophenyl)-1,2-diphenyloct-1-ene (9c)

Yield, 54%; brown crystals; mp 78–80 °C; IR (film): 2124 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.83 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.17–1.54 [m, 8H, $(CH_2)_4$], 2.45 (t, 2H, J = 7.6 Hz, C≡C–CH_2), 6.69 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-3, H-5), 6.87 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-2, H-6), 7.01–7.40 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{26}H_{27}N_3$: C, 81.85; H, 7.13; N, 11.01. Found: C, 81.78; H, 7.31; N, 10.82.

5.12. (*Z*)-1-(4-Azidophenyl)-1,2-diphenyldec-1-ene (9d)

Yield, 56%; brown crystals; mp 72–74 °C; IR (film): 2121 (N_3) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.86 (t, 3H, J = 7.0 Hz, CH_2CH_3), 1.17–1.40 [m, 12H, $(CH_2)_6$], 2.42 (t, 2H, J = 7.6 Hz, C≡C–CH_2), 6.68 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-3, H-5), 6.86 (d, 2H, J = 8.2 Hz, 4-azidophenyl H-2, H-6), 7.10–7.39 (m, 10H, phenyl hydrogens). Anal. Calcd for $C_{28}H_{31}N_3$: C, 82.11; H, 7.63; N, 10.26. Found: C, 81.80; H, 7.93; N, 10.50.

6. 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.[13]

7. In vitro cyclooxygenase (COX) inhibition assay

The ability of the test compounds listed in 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, USA) according to our previously reported method.[13]

8. Anti-inflammatory assay

Anti-inflammatory activity was performed using a method described by Winter et al.[14]

9. Analgesic assay

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

Acknowledgements

We are grateful to (i) the Canadian Institutes of Health Research (CIHR) (MOP-14712) for financial support of this research, (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.), and (iii) Robert McDonald of the Department of Chemistry, University of Alberta for acquiring the X-ray crystal structure data.

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7. Crystal data for (***Z***)-**8a**: Molecular formula: $C_{22}H_{21}NO_2S$, formula weight: 363.46, crystal system: monoclinic, space group: $P2_1/n$ (14) with unit cell dimensions $a = 11.8998$ (14) Å, $b = 5.4926$ (7) Å, $c = 29.4777$ (4) Å, $\beta = 94.201$ (2)° $V = 1921.5$ (4) Å^3, $Z = 4$, $\rho = 1.256\,g\,cm^{-3}$, $\mu = 0.184\,mm^{-1}$. A crystal fragment of approximate dimensions (mm^3) $0.46 \times 0.26 \times 0.10$ was mounted in a nonspecific orientation on Bruker PLATFORM/SMART 1000 CCD diffractometer. All intensity measurements were performed using MoKα radiation ($\lambda = 0.71073$ Å) with a graphite crystal incident beam monochromator. The intensity data were collected at −80° using an ω scan (0.2°) (15 s exposures). A total 3924 independent reflections were collected to a maximum 2θ limit at 52.88°. The structure was solved by Patterson search/structure expansion methods (DIRDIF-99). Refinement of atomic parameters was carried out by using full-matrix least-squares on F^2 (SHELXL-93), giving final agreement factor (R indices) of $R_1 = 0.0559$ and $wR_2 = 0.1397$. Crystallographic data (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 249140. Copies of the data can be obtained free of charge at http://www.ccdc.cam.ac.uk.
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