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Design of acyclic triaryl olefins: a new class of potent and selective cyclooxygenase-2 (COX-2) inhibitors

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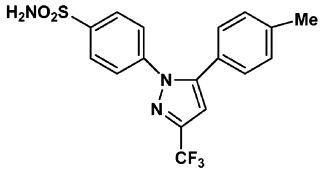
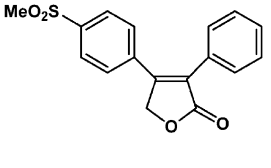
Abstract—A new class of acyclic 1,1-diphenyl-2-(4-methylsulfonylphenyl)-2-alkyl-1-ethenes were synthesized, via a short two-step McMurry olefination reaction and then oxidation of the thiomethyl intermediate using Oxone®, in 62–76% yield. The title compounds possess identical C-1 phenyl substituents which precludes the possibility of (*Z*)- and (*E*)-stereoisomers. 1,1-Diphenyl-2-(4-methylsulfonylphenyl)hex-1-ene exhibited highly potent ($IC_{50} = 0.014$ μM) and selective COX-2 (Selectivity Index >7142) inhibitory activity.

Nonsteroidal antiinflammatory drugs (NSAIDs) are invaluable agents for the treatment of rheumatoid arthritis and osteoarthritis. Inhibition of the cyclooxygenase (COX) pathway is a hallmark feature of virtually all marketed NSAIDs. However, nonselective COX inhibition by NSAIDs such as indomethacin and ibuprofen can cause mechanism based side effects including dyspepsia and gastrointestinal ulceration/bleeding.[1] The recently introduced selective COX-2 inhibitors celecoxib (**1**) and rofecoxib (**2**) elicit efficient antiinflammatory-analgesic activities and less adverse gastrointestinal side effects.[2,3] Selective COX-2 inhibitors are also proving to be very useful in the prophylactic treatment of a wide variety of cancers and neurodegenerative disorders.[4]

Elucidation of the X-ray crystal structure of the diarylheterocyclic celecoxib analogue SC-558 docked in the active site of murine COX-2 has drastically reduced the time required to design novel selective COX-2 inhibitor 'lead-compounds'.[5] The vast majority of tricyclic selective COX-2 inhibitors belong to a diarylheterocyclic or diarylcarbocyclic class.[6,7] The key structural features present in celecoxib and rofecoxib include (i) two vicinal diaryl moieties that are attached to a central heterocyclic ring scaffold (a 5-membered pyrazole in celecoxib and a 5-membered furanone in rofecoxib) and (ii) either a *para*-SO_2NH_2 or a *para*-SO_2Me substituent on one of the phenyl rings that inserts into a secondary pocket that is present in the COX-2, but not COX-1, active site. Resveratrol (**3**) [(*E*)-1-(3,5-dihydroxyphenyl)-2-(4-hydroxyphenyl)ethene] is a naturally occurring acyclic *trans* olefin that exhibits COX-1 selectivity and good chemopreventive properties,[8] whereas the estrogen receptor antagonist tamoxifen (**4**), is an acyclic triaryl olefin.[9,10] As part of our ongoing research we designed a group of simple acyclic triaryl olefinic compounds as selective COX-2 inhibitors, that lack the traditional central heterocyclic or carbocyclic ring template. This novel class of triaryl olefins may provide a clinically acceptable antiinflammatory-analgesic agent that is non-ulcerogenic.



Celecoxib (1)



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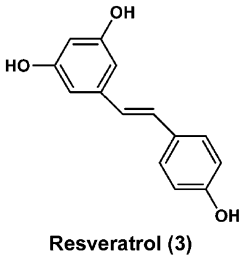
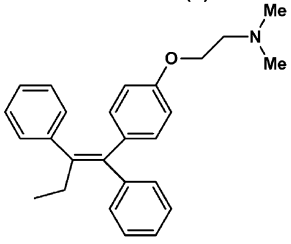


Resveratrol (3)



Tamoxifen (4)

Keywords: Acyclic olefins; Cyclooxygenase-2; Anti-inflammatory.
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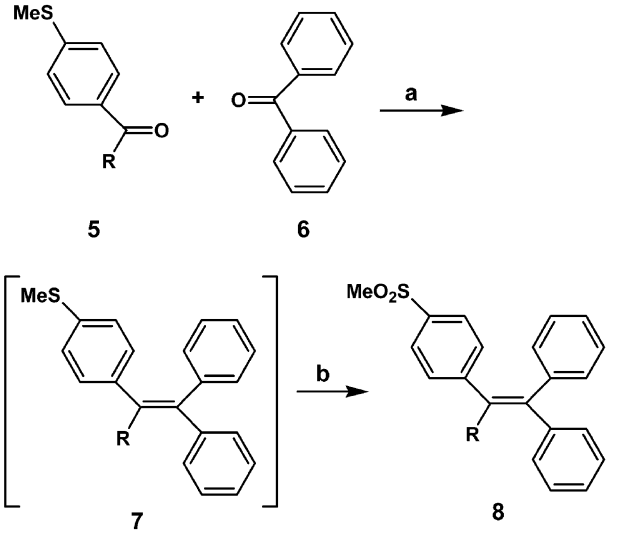
The stereochemical disposition of aryl/alkyl substituents relative to the C=C bond to which they are attached controls COX-2 inhibitory potency and selectivity where the function of the C=C bond is to provide the necessary substituent geometry about the C=C bond that allows an optimal protein-ligand binding interaction in the COX-2 active site. Accordingly, we used a simple chemical drug design approach to synthesize a novel class of acyclic triphenyl olefins **8** with a SO_2Me group at the *para*-position of one of the phenyl rings (C-2) where the alkyl substituent chain length at the C-2 position was varied to modulate COX-2 inhibitory potency and selectivity.

The preparation of compounds **8** is outlined in Scheme 1. Using a McMurry olefination reaction, intermediates **7** were generated in situ by reductive crossed-coupling of ketones **5** (prepared in 60–96% yield by Friedel–Crafts acylation of thioanisole) and benzophenone **6**. Subsequent oxidation of the methylthio intermediates **7** with Oxone® (potassium peroxymonosulfate) afforded the target acyclic 1,1,2-triaryl-2-alkyl-1-ethenes **8** in 62–76% yield.[11–13]

The in vitro enzyme immuno assay data (Table 1) showed that **8a** ($R = CH_3$) was essentially a nonselective COX inhibitor. As alkyl chain length was increased, COX-2 inhibitory potency and selectivity increased drastically with **8c** ($R = C_4H_9$) exhibiting excellent COX-2 inhibitory potency and selectivity (COX-2 $IC_{50} = 0.014$ μM; selectivity index > 7142), being 4-fold more potent and 17-fold more selective than celecoxib, or 30-fold more potent and 6-fold more selective than rofecoxib. A further increase in alkyl chain length (**8d**, $R = C_5H_{11}$; **8e**, $R = C_6H_{13}$) decreased COX-2 selectivity dramatically. Although **8f** ($R = C_9H_{19}$) showed good COX-2 selectivity (COX-2 $IC_{50} = 1.1$ μM; COX-1 $IC_{50} > 100$ μM; selectivity index > 90), it was a 19-fold and 2.5-fold less potent COX-2 inhibitor than celecoxib and rofecoxib, respectively. The longest hydrophobic alkyl chain analogue **8g** ($R = n\text{-}C_{15}H_{31}$) inhibited neither the COX-1, or COX-2, ($IC_{50} > 100$ μM) isozyme.



Scheme 1. Reagents and conditions. (a) Zn, $TiCl_4$, THF, reflux 4.5 h, (b) Oxone® (potassium peroxymonosulfate), MeOH, THF, H_2O, 25 °C, 15 h.

Table 1. In vitro COX-1 and COX-2 inhibition assay data for **8a–g**

Compd	R	IC_{50} (μM)[a]		COX-2
		COX-1	COX-2	S.I.[b]
8a	Me	0.47	0.63	0.74
8b	Et	31.6	1.25	25.3
8c	$n\text{-}C_4H_9$	> 100	0.014	> 7142
8d	$n\text{-}C_5H_{11}$	4.76	2	2.4
8e	$n\text{-}C_6H_{13}$	1.68	0.031	54.2
8f	$n\text{-}C_9H_{19}$	> 100	1.10	> 90
8g	$n\text{-}C_{15}H_{31}$	> 100	> 100	—
Celecoxib	—	23	0.057	403
Rofecoxib	—	> 500	0.43	> 1163

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 assay kit (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI, USA) and 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}).

A molecular modeling (docking)[14] study of **8c** in the COX-2 active site (Fig. 1) showed that it binds in the center of the active site such that the $MeSO_2$ group is oriented in the vicinity of the secondary pocket amino acid residues. Due to the presence of the less bulky Val^{523} (compared to Ile^{523} in COX-1), one of the oxygen-atoms of the SO_2Me group forms a hydrogen bond with the N*H* of Phe^{518} (distance = 2.4 Å), the other SO_2Me *O*-atom is hydrogen bonded to a NH_2 (guanidino group) of Arg^{513} (distance = 3.5 Å), and the *S*-atom is positioned about 1.76 Å inside the entrance to the 2°-pocket (Val^{523}). A weak polar interaction was observed between the terminal NH_2 of Gln^{192} and the SO_2Me *S*-atom (distance = 4.6 Å). As expected, the C-1 phenyl ring *cis* to the C-2 methylsulfonylphenyl substituent was oriented towards a hydrophobic pocket composed of Try^{387}, Tyr^{385} and Tyr^{348} at the top of the channel, whereas the C-1 phenyl ring that is *cis* to the C-2 *n*-butyl subsituent undergoes van der Waal's interactions with Ala^{527}, Ser^{530}, Leu^{531} and Ile^{345} (distance less than 5 Å). The distance between the center of the C-1 phenyl ring *cis* to the C-2 *n*-butyl substituent and the O*H* of Ser^{530} is about 4.9 Å. The C-2 *n*-butyl substituent is oriented towards a pocket comprised of Tyr^{355}, Arg^{120}, Leu^{359} and Val^{349}.

Conformational comparisons of the X-ray crystal structure of SC-558 and **8c** docked in the COX-2 active site are shown in Figure 2. The root mean square deviation (RMSD) between these two conformations was ~0.13 Å. It is noteworthy that the vicinal aromatic rings of both SC-558 and **8c** including their sulfonyl groups lie in a common plane. In the case of SC-558, the CF_3 group at the 3-position of the central pyrazole ring binds to a hydrophobic pocket consisting of Met^{113}, Val^{116}, Val^{349}, Tyr^{355}, Leu^{359} and Leu^{531}. In the acyclic triaryl olefin **8c**, it is significant that C-1 phenyl ring and the cis C-2 *n*-butyl substituent occupy the same pocket with the C-1 phenyl ring undergoing a possible cation-π interaction with the NH_2 of a guanidino side chain of Arg^{120} (distance = 6.0 Å). This interaction may have

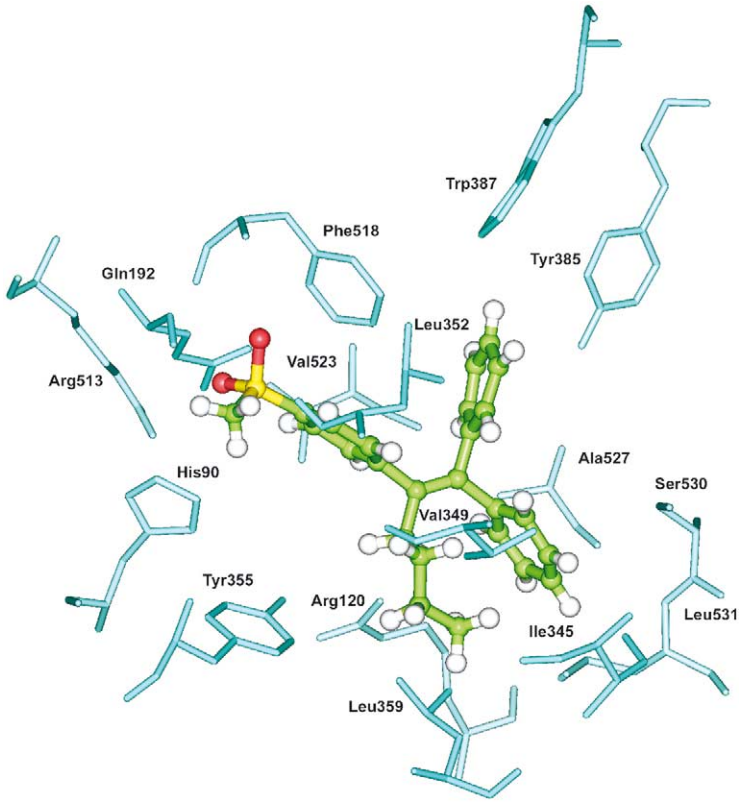


Figure 1. Docking of **8c** in the active site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

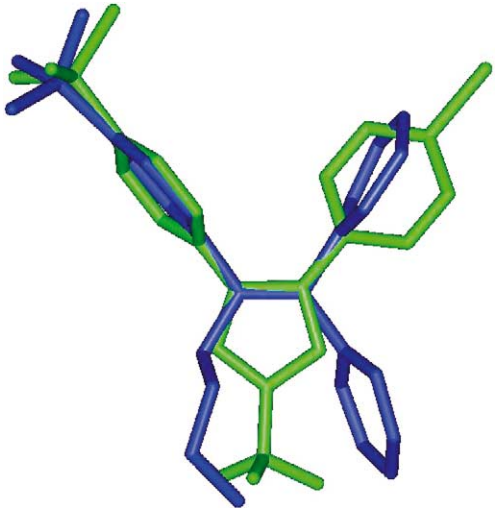


Figure 2. Over lay of binding modes of **8c** (blue) and X-ray crystal structure of SC-558 in the COX-2 active site (green). Hydrogen atoms are not shown for clarity.

important COX-2 selectivity implications by disrupting the salt bridge between Arg^{120} and Glu^{524} at the mouth of the COX-2 binding site.[5,15]

Discovery of this novel class of highly potent and selective COX-2 inhibitory acyclic triaryl olefins illustrates the importance of rational drug design. Accordingly, the presence of a central C=C bond in the place of a traditional central heterocyclic or carbocyclic ring template provides the necessary geometry for the appropriately substituted vicinal diaryl rings to interact favorably with the COX-2 binding site. It is anticipated that this class of 1,1-diphenyl-2-(4-methylsulfonylphenyl)-2-alkyl-1-ethenes (**8**) may also exhibit anticancer activity by a mechanism that is independent of their effect on the COX pathway.

In conclusion, (i) a rational drug design approach was used to identify a new class of achiral acyclic triaryl olefins **8,** that (ii) were synthesized via a short two-step reaction sequence in 62–76% yield, that (iii) possess identical C-1 phenyl substituents which precludes the possibility of (*Z*)- and (*E*)-stereoisomers, which (iv) exhibit highly potent and selective COX-2 inhibitory activity.

Acknowledgements

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References and notes

1. Hernández-Díaz, S.; García Rodríguez, L. A. *Arch. Intern. Med.* **2000**, *160*, 2093.
2. 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. *JAMA* **2000**, *284*, 1247.

3. 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. *N. Engl. J. Med.* **2000**, *343*, 1520.
4. Katori, M.; Majima, M. *Inflamm. Res.* **2000**, *49*, 367.
5. Kurumbail, R. G.; Stevens, A. M.; Gierse, J. K.; McDonald, J. J.; Stegemen, R. A.; Pak, J. Y.; Gildehaus, D.; Miyashiro, J. M.; Penning, T. D.; Seibert, K.; Isakson, P. C.; Stallings, W. C. *Nature* **1996**, *384*, 644.
6. Talley, J. J. *Prog. Med. Chem.* **1999**, *36*, 201.
7. Li, J. J.; Anderson, G. D.; Burton, E. G.; Cogburn, J. N.; Collins, J. T.; Garland, D. J.; Gregory, S. A.; Huang, H. C.; Isakson, P. C.; Koboldt, C. M.; Logusch, E. W.; Norton, M. B.; Perkins, W. E.; Reinhard, E. J.; Seibert, K.; Veenhuizen, A. W. *J. Med. Chem.* **1995**, *38*, 4570.
8. Jang, M.; Cai, L.; Udeani, H. O.; Slowing, K. V.; Thomas, C. F.; Beecher, W. W. C.; Fong, H. H. S.; Farnsworth, N. R.; Kinghorn, A. D.; Mehta, R. G.; Moon, R. C.; Pezzuto, J. M. *Science* **1997**, *275*, 218.
9. Jensen, E. V.; Jordan, V. C. *Clin. Cancer Res.* **2003**, *9*, 1980.
10. Brown, S. D.; Armstrong, R. W. *J. Org. Chem.* **1997**, *62*, 7079.
11. Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608.
12. Habeeb, A. G.; Rao, P. N. P.; Knaus, E. E. *J. Med. Chem.* **2001**, *44*, 2921.
13. Synthesis of 1,1-diphenyl-2-(4-methylsulfonylphenyl)hex-1-ene (**8c**): General Procedure
$TiCl_4$ (1.43 mL, 13 mmol) was added drop wise to a stirred suspension of Zn powder (1.7 g, 26.5 mmol) in dry THF (30 mL), under Ar, at −10 °C, and the reaction was allowed to proceed at reflux for 2 h. A solution of 4-methylthiopentanophenone **5c** (0.68 g, 3.3 mmol) and benzophenone **6** (0.61 g, 3.3 mmol) in THF (65 mL) was added to the cooled suspension of the titanium reagent at 0 °C, and the reaction was allowed to proceed at reflux for 2.5 h. The reaction mixture was cooled to 25 °C, poured into a 10% aqueous K_2CO_3 solution (100 mL), and after vigorous stirring for 5 min, the dispersed insoluble material was removed by vacuum filtration using a Celite 545 pad. The organic layer was separated, the aqueous layer was extracted with EtOAc (3×50 mL), the combined organic fractions were washed with water, the organic fraction was dried (Na_2SO_4), and the solvent was removed in vacuo to afford the olefinic intermediate **7c**. The intermediate **7c** was dissolved in THF-MeOH (1:1, v/v) (10 mL) and a solution of Oxone® (potassium peroxymonosulfate) (4.06 g, 6.6 mmol) in water (20 mL) was added drop wise at 0 °C with stirring. The reaction was allowed to proceed for 15 h at 25 °C with stirring, the solvent was removed in vacuo and water (20 mL) was added to the residue. Extraction with EtOAc (3×30 mL), washing the combined organic extracts with water, drying the organic fraction (Na_2SO_4), and removal of the solvent in vacuo gave a residue that was purified by silica gel flash column chromatography (*n*-hexane–EtOAc, 2:1 v/v) to afford **8c** (0.91 g, 72%) as white needles; mp 79–81 °C; IR (film): 1153, 1327 (SO_2), 1593 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.79 (t, 3H, $J=6.7$ Hz, CH_3), 1.24–1.27 [m, 4H, $(CH_2)_2$], 2.48 (t, 2H, $J=7.3$ Hz, CH_2), 3.03 (s, 3H, SO_2CH_3), 6.84–6.87 (m, 2H, phenyl hydrogens), 7.02–7.04 (m, 3H, phenyl hydrogens), 7.23–7.28 (m, 5H, phenyl hydrogens), 7.31 (d, 2H, $J=8.2$ Hz, 4-methylsulfonylphenyl H-2, H-6), 7.72 (d, 2H, $J=8.2$ Hz, 4-methylsulfonylphenyl H-3, H-5). Anal. calcd for $C_{25}H_{26}O_2S\cdot 1/8H_2O$: C, 76.44; H, 6.68. Found: C, 76.28; H, 6.86.
14. Molecular Modeling (Docking) Studies: Docking experiments were performed using Insight II software Version 2000.1 (Accelrys Inc.) running on a Silicon Graphics Octane 2 R14000A workstation. The coordinates for the X-ray crystal structures of the enzyme COX-2 was obtained from the RCSB Protein Data Bank and hydrogens were added. The ligand molecules were constructed using the Builder module and energy minimized for 1000 iterations reaching a convergence of 0.01 kcal/mol Å. The docking experiment on COX-2 was carried out by superimposing the energy minimized ligand on SC-558 in the PDB file 1cx2 after which SC-558 was deleted. The resulting ligand-enzyme complex was subjected to docking using the Affinity command in the Docking module of Insight II after defining subsets of the enzyme such that residues within 10 Å of the ligand were allowed to relax, while the remainder of the enzyme residues were fixed. The consistent valence force field (CVFF) was employed for all docking purposes. The optimum ligand-enzyme assembly obtained after docking was subjected to a molecular dynamics (MD) simulation using the Discover module Version 2.98 at a constant temperature of 300 K with a 100 step equilibration for over 1000 iterations and a time step of 1 fs using a distance dependent dielectric constant 4r. The ligand-enzyme assembly thus obtained was further minimized for 1000 iterations using the conjugate gradient method until a convergence of 0.001 kcal/mol Å was reached.
15. Greig, G. M.; Francis, D. A.; Falgueyret, J. P.; Ouellet, M. M.; Percival, M. D.; Roy, P.; Bayly, C.; Mancini, J. A.; O'Neill, G. P. *Mol. Pharmacol.* **1997**, *52*, 829.