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Design and synthesis of (*E*)-1,1,2-triarylethenes: novel inhibitors of the cyclooxygenase-2 (COX-2) isozyme

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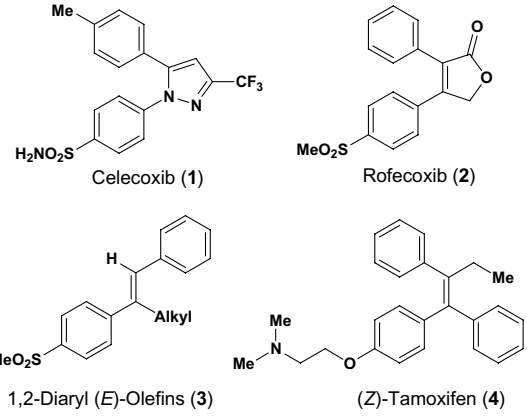
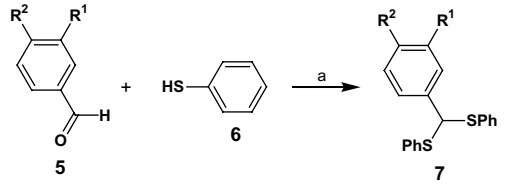
Abstract—A novel class of acyclic 1,1,2-triaryl (*E*)-ethenes was designed that were synthesized via an (*E*)-selective Takeda olefination reaction. Among the group of compounds evaluated, (*E*)-2-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)-1-phenylethene (**10c**) emerged as the most potent (COX-2 IC_{50} = 0.0316 μM), and selective (selectivity index > 3164), COX-2 inhibitor.

Celecoxib (**1**) and rofecoxib (**2**), which belong to a vicinal diarylheterocyclic class of selective COX-2 inhibitors, exhibit excellent anti-inflammatory and analgesic activities with reduced gastrointestinal side effects. The discovery of these novel anti-inflammatory-analgesic agents was facilitated by a knowledge of the structural differences and similarities between the COX-1 and COX-2 isozymes obtained from X-ray crystal structure data.[1,2] Recent studies indicate that selective COX-2 inhibitors may have therapeutic applications for the treatment, and/or prophylactic prevention, of certain types of cancer and neurodegenerative disorders.[3] Compounds possessing an acyclic diaryl, or triaryl, olefin template are known to exhibit a variety of therapeutic activities depending on their functional or structural features/substituents. In this regard, we recently reported acyclic 2-alkyl-1,2-diaryl (*E*)-olefins (**3**) possessing a *trans*-stilbenoid structure with a 4-methylsulfonylphenyl substituent at the C-2 position that exhibit selective cyclooxygenase-2 (COX-2) inhibition,[4] and it is known that the acyclic 2-alkyl-1,1,2-triaryl (*Z*)-olefin tamoxifen (**4**) is a selective estrogen receptor antagonist widely used for the treatment of hormone-responsive breast cancers.[5,6] As part of our ongoing program to design new central scaffolds/templates for the design of selective COX-2 inhibitors, we describe herein the synthesis and biological evaluation of a novel class of 1,1,2-triaryl (*E*)-ethenes (**10**) possessing a *p*-$MeSO_2$ COX-2 pharmacophore on the C-1 phenyl ring.



The aromatic aldehydes **5** (R^1 = H, F; R^2 = H, Me, SMe, F, Cl) were converted to the corresponding thioacetals **7** by treatment with thiophenol (**6**) in the presence of $BF_3{\cdot}OEt_2$ (Scheme 1).[7,8]



Scheme 1. Reagents and conditions: (a) $BF_3{\cdot}OEt_2$, $CHCl_3$, 25 °C, 1 h.

Keywords: COX-2 inhibitors; COX-2 selectivity; (*E*)-ethenes.
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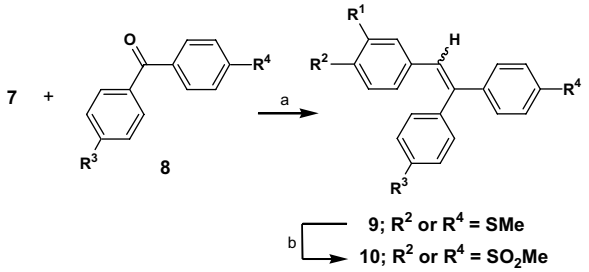

Scheme 2. Reagents and conditions: (a) Cp_2TiCl_2, molecular sieves 4A, Mg, $P(OEt)_3$, THF, 25 °C, 15 h; (b) Oxone® (potassium peroxymonosulfate), MeOH, THF, H_2O, 25 °C, 15 h.

The intermediate *p*-methylthiophenylethenes **9** (R^1 = H, F; R^2 = H, Me, SMe, F, Cl; R^3 = H, Me, F, Cl; R^4 = Me, SMe, F, Cl) were generated in situ by a $Cp_2Ti[P(OEt)_3]_2$ promoted Takeda olefination reaction of a thioacetal **7** with a diaryl ketone **8** with high (*E*)-selectivity as determined after conversion to the corresponding *p*-methylsulfonylphenylethene product **10** (R^1 = H, F; R^2 = H, Me, SO_2Me, F, Cl; R^3 = H, Me, F, Cl; R^4 = Me, SO_2Me, F, Cl) (**10e**, *E*:*Z* ratio = 10.8:1). Repetitive fractional recrystallization of the crude (*E*)- and (*Z*)-isomeric mixture from EtOH (95%, w/v) was carried out until the desired (*E*)-olefin **10** was obtained as a single stereoisomer (Scheme 2).[9,10]

The structures of the ethene products **10a–h** were consistent with their spectral and microanalytical data. The absolute stereochemistry of (*E*)-**10e** (R^1 = H, R^2 = Cl, R^3 = H, R^4 = SO_2Me) was established by a single crystal X-ray analysis (Fig. 1).[11]

Although the mechanism for (*E*)-stereoselectivity of this olefination reaction is still unclear, steric factors associated with the oxatitanacyclobutane complex (**11**) in the transition state seem to be important, which could induce (*E*)-stereocontrol due to the preferential formation of a sterically favored oxatitanacyclobutane complex (**11a**) in which the two bulkier neighboring (a cyclopentadienyl ring and an unsubstituted or substituted phenyl ring) groups are more distal to each other. In contrast, formation of the (*Z*)-isomer would involve a sterically disfavored oxatitanacyclobutane complex

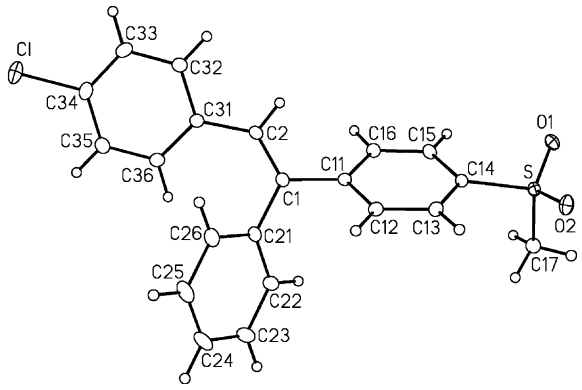

Figure 1. X-ray crystal structure of (*E*)-2-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)-1-phenylethene (**10e**).

(**11b**), where these two neighboring groups are very close to each other that would result in an extremely high steric hindrance (Fig. 2).

The in vitro COX-1/COX-2 isozyme immunoassay[12] data acquired (Table 1) showed that (*E*)-**10a** (R^1 = R^2 = R^3 = H; R^4 = SO_2Me) is a nonselective cyclooxygenase (COX) inhibitor (COX-2 IC_{50} = 0.31 μM; COX-1 IC_{50} 0.14 μM). Incorporation of a methyl group at the *p*-position of the C-2 phenyl ring in (*E*)-**10b** (R^1 = H; R^2 = Me; R^3 = H; R^4 = SO_2Me) increased COX-2 inhibitory potency (IC_{50} = 0.12 μM) and selectivity (selectivity index > 833) considerably. When the *p*-methyl group was replaced by a *p*-fluoro substituent, COX-2 inhibitory potency and selectivity increased

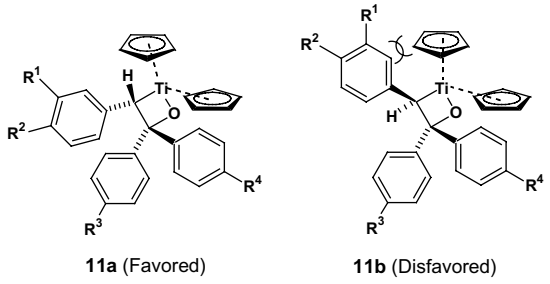

Figure 2. Proposed mechanism for (*E*)-stereoselection involving a favored oxatitanacyclobutane complex (**11a**) in the transition state.

Table 1. In vitro COX-1/COX-2 isozyme immunoassay data for ethenes **10a–h**

Compound	R^1	R^2	R^3	R^4	COX-1 IC_{50} (μM)[a]	COX-2 IC_{50} (μM)[a]	COX-2 SI[b]
(*E*)-**10a**	H	H	H	SO_2Me	0.14	0.31	0.45
(*E*)-**10b**	H	Me	H	SO_2Me	>100	0.12	>833
(*E*)-**10c**	H	F	H	SO_2Me	>100	0.0316	> 3164
(*E*)-**10d**	F	F	H	SO_2Me	>100	0.97	>103
(*E*)-**10e**	H	Cl	H	SO_2Me	>100	0.1138	> 878
10f	H	SO_2Me	Me	Me	>100	31.6	>3
10g	H	SO_2Me	F	F	>100	32.0	>3
10h	H	SO_2Me	Cl	Cl	>100	2.0	>50
Celecoxib	—	—	—	—	33.1	0.07	472
Rofecoxib	—	—	—	—	>100	0.50	>200

[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}).

significantly with (*E*)-**10c** (R^1 = H; R^2 = F; R^3 = H; R^4 = SO_2Me) (COX-2 IC_{50} = 0.0316 μM; COX-2 selectivity index > 3164) being 2.2-fold more potent and 6.7-fold more selective than celecoxib (**1**), or 16-fold more potent and 15.8-fold more selective than rofecoxib (**2**). However, the presence of an additional fluoro substituent at the C-2 phenyl ring as with compound (*E*)-**10d** (R^1 = R^2 = F; R^3 = H; R^4 = SO_2Me) resulted in a reduction in COX-2 inhibitory potency (COX-2 IC_{50} = 0.97 μM). The mono chloro analog (*E*)-**10e** (R^1 = H; R^2 = Cl; R^3 = H; R^4 = SO_2Me) and the *p*-methyl analog (*E*)-**10b** were equipotent COX-2 inhibitors. It is interesting to note that, a significant reduction in COX-2 potency was observed, when the SO_2Me COX-2 pharmacophore was placed at the *p*-position of the C-2 phenyl ring of the central C=C. In this regard **10f** and the related analogs **10g–h**, having a C-2 *p*-methylsulfonylphenyl substituent, were much less potent (IC_{50} = 2–32 μM range), and less selective COX-2 inhibitors (SI = >3 to >50 range) than regioisomeric compounds **10a–e**, having a C-1 *p*-methylsulfonylphenyl substituent (COX-2 IC_{50} range = 0.0316–0.97 μM range; SI = 0.45 to >3164 range).

A molecular modeling (docking) study[12] of the most stable ligand–enzyme complex of **10c** (Fig. 3) showed that this ligand binds in the center of the COX-2 binding site such that the C-1 *p*-$MeSO_2$-phenyl substituent is positioned in the vicinity of the COX-2 secondary pocket where it is surrounded by Phe^{518}, Arg^{513}, Gln^{192}, Ser^{353}, and Val^{523}. One of the oxygen atoms of the SO_2Me group undergoes a *H*-bonding interaction with the backbone N*H* of Phe^{518} (distance = 2.16 Å), whereas the other oxygen atom is close to the guanidine side chain (NH_2) of Arg^{513} (distance = 2.71 Å). The C-2 *p*-fluorophenyl substituent is oriented in a region comprised of Ala^{527}, Ser^{530}, Leu^{531}, Leu^{534}, Val^{349}, and Ile^{345}. Interestingly, there is a *H*-bonding interaction between the fluorine-atom present at the *p*-position of the C-2 phenyl ring and the O*H* of Ser^{530} (distance = 2.4 Å) that is the acetylation site of aspirin. The geminal unsubstituted C-1 phenyl ring was oriented toward the mouth of the primary COX-2 binding site where it interacts with Tyr^{355}, Arg^{120}, and Leu^{359}.

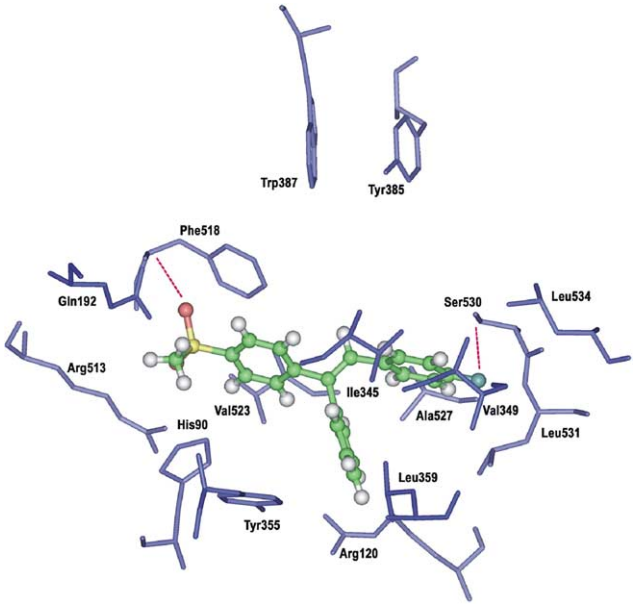

Figure 3. Docking of (*E*)-**10c** in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

In conclusion, this investigation shows that, (i) a novel group of 1,1,2-triaryl (*E*)-ethenes can be synthesized via an (*E*)-selective Takeda olefination reaction, (ii) COX-1/COX-2 isozyme inhibition structure–activity studies identified (*E*)-2-(4-fluorophenyl)-1-(4-methylsulfonylphenyl)-1-phenylethene (**10c**) as a highly potent (IC_{50} = 0.0316 μM), and selective (selectivity index >3164), COX-2 inhibitor, (iii) COX-2 inhibitory potency and selectivity for this 1,1,2-triarylethene template is sensitive to appropriate placement of the olefinic substituents and their relative stereochemistry with respect to C=C, and (iv) the function of the carbon–carbon double bond is to provide necessary substituent geometry for an optimal enzyme–ligand binding interaction within the COX-2 binding site.

Acknowledgements

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8. Synthesis of thioacetals **7**. General procedure. Boron trifluoride etherate (21.3 g, 150 mmol) was added slowly to a solution of the aromatic aldehyde **5** (R^1 = H, F; R^2 = H, Me, SMe, F, Cl) (150 mmol) and thiophenol (34.6 g, 314.5 mmol) in $CHCl_3$ (150 mL) at 0 °C. The reaction mixture was stirred for 1 h at 25 °C prior to quenching with H_2O (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). Washing the combined organic extracts with an aqueous 1 M NaOH solution, drying the organic fraction (Na_2SO_4) and

removal of the solvent in vacuo gave a residue, which was recrystallized from *n*-hexane–$CHCl_3$ (3:1, v/v) to afford the respective thioacetal **7** in 75–82% overall yield. The physical, spectroscopic and microanalytical data for the thioacetal **7c** are listed below; 1-[Bis(phenylthio)methyl]-4-fluorobenzene (**7c**). Yield, 75%; white crystals; mp 54–56 °C; IR (film): 3058, 3075 (CH_{arom}) cm^{-1}; ^1H NMR ($CDCl_3$): δ 5.43 (s, 1H, C*H*), 6.96 (d, J_{HCCF} = 8.5 of d, J_{HCCH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.24–7.37 (m, 12H, phenyl hydrogens and 4-fluorophenyl H-2, H-6). Anal. Calcd for $C_{19}H_{15}FS_2$: C, 69.90; H, 4.63. Found: C, 69.80; H, 4.37.

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10. Synthesis of 1,1,2-triaryl ethenes **10**. General procedure. $P(OEt)_3$ (3.59 g, 21.6 mmol) was added slowly to a stirred suspension of Cp_2TiCl_2 (2.69 g, 10.8 mmol), powdered molecular sieves 4A (0.7 g) and Mg turnings (0.29 g, 12 mmol) in dry THF (10 mL), under Ar at 25 °C. After the addition was complete, the reaction mixture was stirred for 3 h at 25 °C. A solution of the thioacetal (**7**, R^1 = H, F; R^2 = H, Me, SMe, F, Cl) (3.3 mmol) in THF (3 mL) was added to the low-valent titanium reagent at 25 °C. After stirring for 5–10 min, a solution of the diaryl ketone (**8**, R^3 = H, Me, F, Cl; R^4 = Me, F, Cl, SMe) (3 mmol) in THF (3 mL) was added dropwise to the reaction mixture and the mixture was stirred for 12 h at 25 °C. An aqueous 1 M NaOH solution (10 mL) was added to the reaction mixture that was stirred vigorously for 5 min. The dispersed insoluble material in the reaction mixture was removed by vacuum filtration through a pad of Celite 545. The organic layer was separated and the aqueous layer was extracted with ether (3 × 10 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, and then flash column chromatography (*n*-hexane–EtOAc, 49:1 v/v) to eliminate the unreacted starting materials and byproducts, afforded the respective *p*-methylthiophenyl (*E*,*Z*)-ethene (**9**, R^1 = H, F; R^2 = H, Me, SMe, F, Cl; R^3 = H, Me, F, Cl; R^4 = Me, F, Cl, SMe). The respective *para*-methylthiophenyl (*E*,*Z*)-ethene (**9**) 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 dropwise at 0 °C with stirring. The reaction was allowed to proceed for 15 h at 25 °C, the solvent was removed in vacuo, water (20 mL) was added to the residue, and this mixture 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, flash column chromatography (*n*-hexane–EtOAc, 3:1 v/v), and then repetitive fractional recrystallizations (two or three) of each (*E*):(*Z*)-ethene mixture (**10**) from EtOH (95%, w/v) afforded the respective *p*-methylsulfonylphenyl (*E*)-ethene (**10**, R^1 = H, F; R^2 = H, Me, SO_2Me, F, Cl; R^3 = H, Me, F, Cl; R^4 = Me, F, Cl, SO_2Me) exclusively in 59–66% overall isolated yield. The physical, spectroscopic and microanalytical data for (*E*)-**10c** are listed below. (*E*)-2-(4-flourophenyl)-1-(4-methylsulfonylphenyl)-1-phenylethene (**10c**). Yield, 62%; white crystals; mp 140–142 °C; IR (film): 1143, 1324 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.12 (s, 3H, SO_2CH_3), 6.86 (d, J_{HCCF} = 8.8 Hz of d, J_{HCCH} = 8.8 Hz, 2H, 4-fluorophenyl H-3, H-5), 6.97 (d, J_{HCCH} = 8.8 Hz of d, J_{HCCCF} = 5.4 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.01 (s, 1H, C=C*H*), 7.24–7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.33–7.35 (2H, phenyl H-2, H-6), 7.40 (d, 2H, *J* = 8.2 Hz, 4-methylsulfonylphenyl H-2, H-6), 7.90 (d, 2H, *J* = 8.2 Hz, 4-methylsulfonylphenyl H-3, H-5). Anal. Calcd for $C_{21}H_{17}FO_2S$: C, 71.57; H, 4.86. Found: C, 71.39; H, 4.83.
11. Crystal data for (*E*)-2-(4-chlorophenyl)-1-(4-methylsulfonylphenyl)-1-phenylethene (**10e**) (excluding structure factors) have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 250894. Copies of the data can be obtained free of charge by application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax: 44-0-1223-336033 or, e-mail: http://deposit@ccdc.cam.ac.uk or, http://www.ccdc.cam.uk).
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