Synthesis and Structure−Activity Relationship Studies of 1,3-Diarylprop-2-yn-1-ones: Dual Inhibitors of Cyclooxygenases and Lipoxygenases

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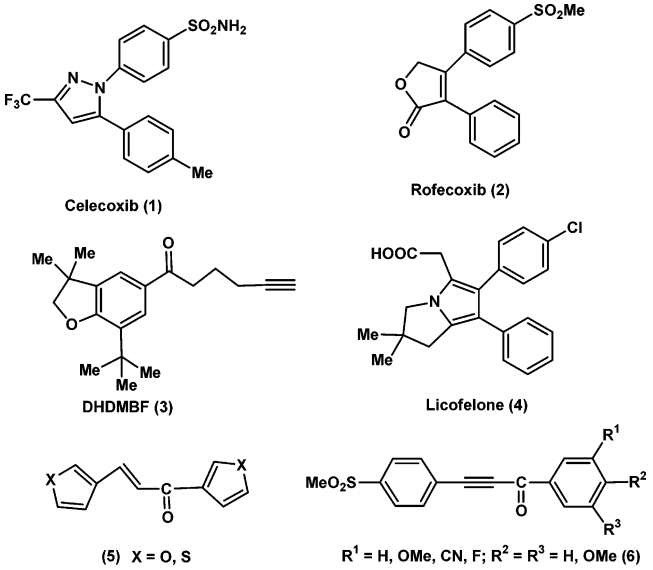
A group of 1,3-diarylprop-2-yn-1-ones (**13**, **17**, **23**, **26** and **27**) possessing a C-3 *p*-SO_2Me COX-2 pharmacophore were designed, synthesized and evaluated as potential dual inhibitors of cyclooxygenase-1/2 (COX-1/2) and 5/15-lipoxygenases (5/15-LOX) that exhibit vivo antiinflammatory and analgesic activities. Among this class of compounds, 3-(4-methanesulfonylphenyl)-1-(4-fluorophenyl)prop-2-yn-1-one (**13h**) was identified as a potent and selective inhibitor of COX-2 (COX-2 $IC_{50} = 0.1$ μM; SI = 300), being 5-fold more potent than rofecoxib (COX-2 $IC_{50} = 0.5$ μM; SI > 200). In a rat carrageenan-induced paw edema assay **13h** exhibited moderate antiinflammatory activity (26% inhibition of inflammation) at 3 h after administration of a 30 mg/kg oral dose. A related dual COX-1/2 and 5/15-LOX inhibitor 3-(4-methanesulfonylphenyl)-1-(4-cyanophenyl)prop-2-yn-1-one (**13g**, COX-1 $IC_{50} = 31.5$ μM; COX-2 $IC_{50} = 1.0$ μM; SI = 31.5; 5-LOX $IC_{50} = 1.0$ μM; 15-LOX $IC_{50} = 3.2$ μM) exhibited more potent antiinflammatory activity ($ED_{50} = 90$ mg/kg), being superior to the reference drug aspirin ($ED_{50} = 129$ mg/kg). Within this group of compounds 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**) emerged as having an optimal combination of in vitro COX-1/2 and 5/15-LOX inhibitory effects (COX-1 $IC_{50} = 9.2$ μM; COX-2 $IC_{50} = 0.32$ μM; SI = 28; 5-LOX $IC_{50} = 0.32$ μM; 15-LOX $IC_{50} = 0.36$ μM) in conjunction with a good antiinflammatory activity ($ED_{50} = 35$ mg/kg) compared to the reference drug celecoxib ($ED_{50} = 10.8$ mg/kg) when administered orally. A molecular modeling study where **13e** was docked in the COX-2 binding site indicated the C-1 *p*-*i*-Pr group was positioned within a hydrophobic pocket (Phe205, Val344, Val349, Phe381 and Leu534), and that this positioning of the *i*-Pr group facilitated orientation of the C-3 *p*-SO_2Me COX-2 pharmacophore such that it inserted into the COX-2 secondary pocket (His90, Arg513, Ile517 and Val523). A related docking study of **13e** in the 15-LOX binding site indicates that the C-3 *p*-SO_2Me COX-2 pharmacophore was positioned in a region closer to the catalytic iron site where it undergoes a hydrogen bonding interaction with His541 and His366, and that the C-1 *p*-*i*-Pr substituent is buried deep in a hydrophobic pocket (Ile414, Ile418, Met419 and Ile593) near the base of the 15-LOX binding site.

Introduction

Introduction of selective cyclooxygenase-2 (COX-2) inhibitors (see structures in Chart 1) such as celecoxib (Celebrex, **1**) and rofecoxib (Vioxx, **2**) in the late 1990s heralded the start of a new era for the treatment of inflammatory conditions such as rheumatoid arthritis (RA) and osteoarthritis (OA).[1,2] However, the recent withdrawal of rofecoxib, and subsequently valdecoxib (Bextra), due to their adverse cardiovascular side effects clearly delineates the need to develop antiinflammatory agents exhibiting reduced gastrointestinal (GI) and cardiovascular side effects.[3,4] It is well established that conventional nonsteroidal antiinflammatory drugs (NSAIDs) and selective COX-2 inhibitors decrease the bioconversion of arachidonic acid (AA) to proinflammatory prostaglandins (PGs) by inhibiting the COX pathway.[5] Alternatively, arachidonic acid can also undergo bioconversion to proinflammatory lipid mediators through the lipoxygenase (LOX) pathway. For example, leukotrienes (LTs) produced via the 5-LOX enzyme catalyzed pathway are known to play a role in the pathogenesis of inflammatory and allergic disorders.[6] Zileuton was the first 5-LOX inhibitor used in the chronic treatment of asthma.[7] The related isozyme 15-LOX is linked to cardiovascular complications since it is known to participate in oxidative modification of low-density lipoproteins (LDL) leading to the development of atherosclerosis.[8]

Chart 1. Representative Examples of COX and LOX Inhibitors



Accordingly, development of dual inhibitors of cyclooxygenases (COXs) and lipoxygenases (LOXs) have shown promising results.[9,10] In this regard, the dual COX/LOX inhibitor dihydrodimethylbenzofuran (DHDMBF, **3**) showed excellent antiinflammatory activity with reduced GI side effects, whereas licofelone (**4**) a dual COX/LOX inhibitor has been effective in

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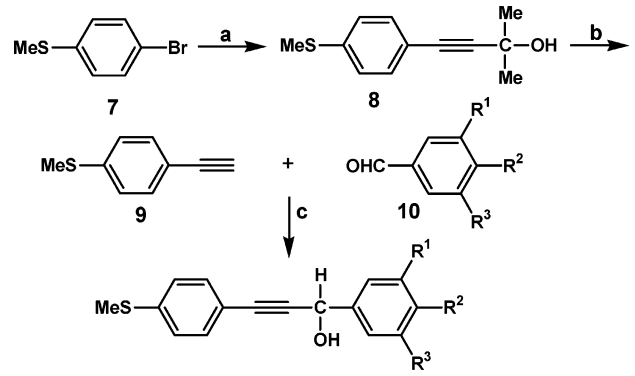
Scheme 1[a]



	R^1	R^2	R^3
13a	H	H	H
13b	H	Me	H
13c	H	*n*-Pr	H
13d	H	*n*-Bu	H
13e	H	*i*-Pr	H
13f	H	CF_3	H
13g	H	CN	H
13h	H	F	H
13i	F	F	H
13j	H	OMe	H
13k	H	OH	H
13l	OMe	H	H
13m	OH	H	H
13n	OMe	OMe	H
13o	OMe	OMe	OMe
13p	H	COOMe	H

f

[a] Reagents and conditions: (a) triethylamine, 2-methyl-3-butyn-1-ol, $PdCl_2(PPh_3)_2$, CuI, 70−75 °C, 6 h; (b) benzene, NaH, 105−110 °C, 1 h; (c) THF, −78 °C, *n*-BuLi, and then at −78 °C to 25 °C overnight; (d) acetone, MnO_2, 25 °C, 2−3 h; (e) 1,4-dioxane, aqueous Oxone, 25 °C, 3−4 h; (f) BBr_3, CH_2Cl_2, −5−0 °C, 1 h.

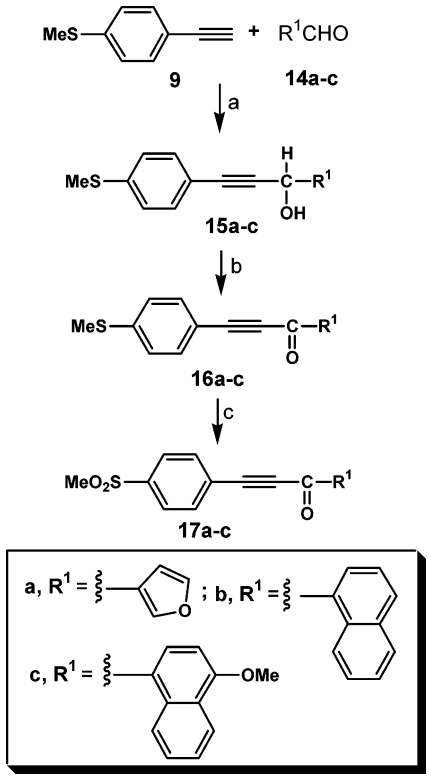
the treatment of OA exhibiting reduced GI toxicity compared to conventional NSAIDs.[11,12] In addition, recent studies have also shown that dual inhibitors of COX/LOX could be useful as tumor suppressor agents in the treatment of prostate and colon cancers.[13,14]

Other studies have shown that compounds possessing a propenone moiety as represented by **5** exhibit dual COX/LOX inhibition,[15] and that a novel class of 1,3-diphenylprop-2-yn-1-ones (**6**) reported previously possessing a central propynone moiety constitutes a suitable template for the design of dual COX/LOX inhibitors.[16] As part of our ongoing research program, we describe herein the design, synthesis and more extensive structure−activity relationship (SAR) studies for this new class of 1,3-diarylprop-2-yn-1-ones as dual inhibitors of COX/LOX enzymes exhibiting in vivo antiinflammatory and analgesic activities.

Chemistry

A variety of synthetic approaches have been used successfully for the preparation of acetylenic ketones [17−19] The synthetic

Scheme 2[a]

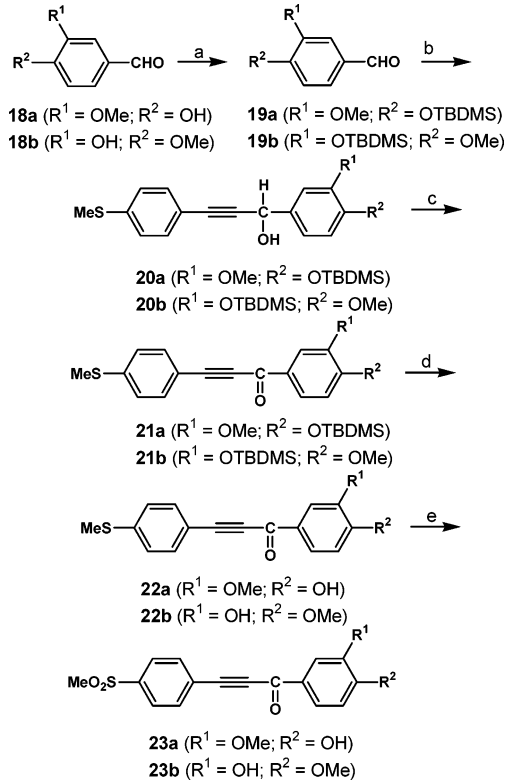


[a] Reagents and conditions: (a) THF, −78 °C, *n*-BuLi, −78 °C to 25 °C overnight; (b) acetone, MnO_2, 25 °C, 2−3 h; (c) 1,4-dioxane, aqueous Oxone, 25 °C, 3−4 h.

strategies used in this study to prepare the target 1,3-diarylprop-2-yn-1-ones (**13a**−**p**, **17a**−**c**, **23a**,**b**, **26a**−**c** and **28**) are illustrated in Schemes 1−4. Sonogashira coupling of 4-bromothioanisole (**7**) with 2-methyl-3-butyn-1-ol in the presence of triethylamine (Et_3N), CuI and a Pd(0) catalyst [$PdCl_2(PPh_3)_2$] afforded the protected *p*-methylsulfanylphenylacetylene (**8**) in 70−75% yield (Scheme 1). Subsequent removal of the 2-propanol moiety was effected using NaH to afford 1-ethynyl-4-methylsulfanylbenzene (**9**) in 40−55% yield. The 1,3-diphenylprop-2-yn-1-ols (**11**) were synthesized by the condensation of **9** with a substituted-benzaldehyde (**10**) in the presence of *n*-butyllithium (40−58%).[20] Subsequent oxidation of **11** using activated manganese dioxide (MnO_2) afforded the corresponding 1,3-diphenylprop-2-yn-1-one (**12**) in 44−56% yield as shown in Scheme 1. Subsequent oxidation of **12** using an aqueous solution of Oxone afforded the target 1,3-diphenylprop-2-yn-1-ones (**13a**−**j**, **13l** and **13n**−**p**) possessing a C-3 *p*-SO_2Me substituent in good yield (60−90%). Compounds **13k** and **13m** possessing a C-1 hydroxyl substituent were prepared by the *O*-demethylation of **13j** and **13l** in the presence of boron tribromide (50−55%) as shown in Scheme 1. Compounds **17a**−**c** possessing a R^1 furanyl (**17a**), naphthyl (**17b**) or a methoxynaphthyl (**17c**) substituent were prepared as shown in Scheme 2, where the respective aldehydes (**14a**−**c**) were condensed with **9** in the presence of *n*-butyllithium to prepare **15a**−**c** (58−62%). Subsequent oxidation of the alcohols **15a**-c using MnO_2 afforded the ketones **16a**−**c** (52−65%). Oxidation of the SMe moiety in **16a**−**c** using an aqueous solution of Oxone afforded the target SO_2Me products **17a**−**c** (81−88%).

Compounds **23a** and **23b** possessing a C-1 methoxyphenol substituent were prepared as shown in Scheme 3. The *tert*-butyldimethylsilyl ethers (**19a** and **19b**) were prepared by the reaction of the respective phenols (**18a** and **18b**) with *tert*-

Scheme 3[a]



[a] Reagents and conditions: (a) THF, NaH, TBDMSCl, 25 °C, 2−3 h; (b) **9**, THF, −78 °C, *n*-BuLi, −78 °C to 25 °C overnight; (c) acetone, MnO_2, 25 °C, 2−3 h; (d) EtOH, KOH, 25 °C, 1 h; (e) 1,4-dioxane, aqueous Oxone, 25 °C, 3−4 h.

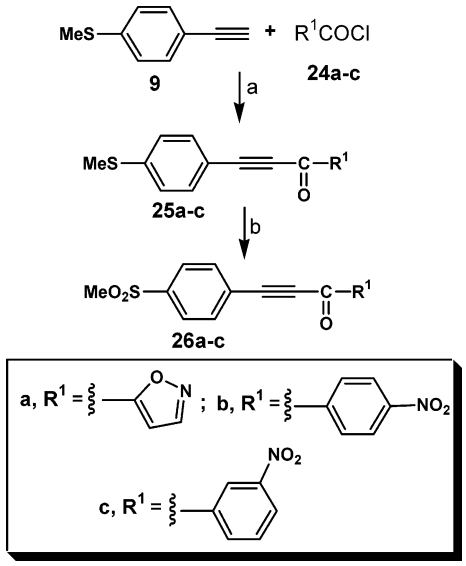
butyldimethylsilyl chloride (TBDMSCl) in the presence of NaH in good yield (65−70%).[21] Subsequent condensation of **19a** or **19b** with **9** in the presence of *n*-BuLi, and then oxidation of the intermediate alcohol using activated MnO_2, afforded the 1,3-diphenylprop-2-yn-1-ones (**21a** and **21b**; 45−54%). The phenolic derivatives **22a** and **22b** were obtained by removal of the *tert*-butyldimethylsilyl protecting group present in **21a** and **21b** using KOH in EtOH (45−52%).[22] Subsequent oxidation of **21a** and **21b** using aqueous Oxone afforded the target SO_2Me products **23a** and **23b** (80−85%) as illustrated in Scheme 3.

The 1,3-diarylprop-2-yn-1-ones **26a**−**c** were prepared using the reactions shown in Scheme 4. The Sonogashira coupling of the terminal alkyne **9** with an acid chloride (**24a**−**c**) using a Pd(0) catalyst [$PdCl_2(PPh_3)_2$], CuI and Et_3N at room temperature afforded the respective product **25a**−**c** (18−25%)[23] possessing a C-3 methylthiophenyl substituent which was subsequently oxidized to the corresponding methanesulfonylphenyl derivatives (**26a**−**c**) in good yield (80−84%) using an aqueous solution of Oxone. Compound **28** was prepared by the oxidation of 1,3-diphenylprop-2-yn-1-one (**27**) using an aqueous solution of Oxone (75%) as shown in Scheme 5.

Results and Discussion

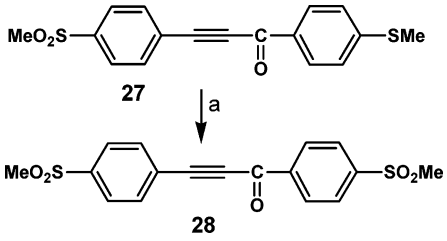
The 1,3-diarylprop-2-yn-1-ones (**13a**−**p**, **17a**−**c**, **23a**,**b**, **26a**−**c**, **27** and **28**) possessing a *p*-SO_2Me COX-2 pharmacophore on the C-3 phenyl ring were evaluated in vitro to determine their COX-1/2 and 5/15-LOX inhibitory activities. The structure−activity relationship (SAR) data acquired for these 1,3-diarylprop-2-yn-1-ones showed that they exhibit a broad range (potent-to-inactive) of COX/LOX inhibitory activities (COX-2 IC_{50} = 0.1 to >100 μM range; COX-1 IC_{50} = 0.2 to >100 μM range; 5-LOX IC_{50} = 0.1 to >10 μM range; 15-LOX IC_{50} = 0.1 to

Scheme 4[a]



[a] Reagents and conditions: (a) THF, 25 °C, $PdCl_2(PPh_3)_2$, CuI, triethylamine 25 °C, 2−3 h; (b) 1,4-dioxane, aqueous Oxone, 25 °C, 3−4 h.

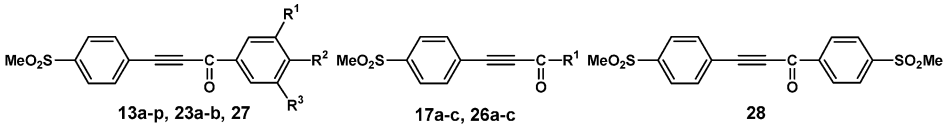
Scheme 5[a]

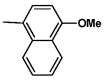


[a] Reagents and conditions: (a) 1,4-dioxane, aqueous Oxone, 25 °C, 3−4 h.

>10 μM range; Table 1). Compound **13a**, having an unsubstituted C-1 phenyl ring was a 10-fold less potent inhibitor of COX-2 (COX-2 IC_{50} = 10 μM) than COX-1, and it did not inhibit either 5- or 15-LOX at a concentration of 10 μM. Introduction of an alkyl substituent (**13b**, R^2 = Me) provided weak COX-2 inhibition and modest COX-2 selectivity (COX-2 IC_{50} = 33.0 μM; SI > 3.0) with no gain in either 5- or 15-LOX inhibition. In contrast, increasing the alkyl chain length **13c** (R^2 = *n*-Pr) provided dual COX and LOX inhibition with a gain in both COX and 5/15-LOX inhibitory potency (COX-1 IC_{50} = 3.2 μM; COX-2 IC_{50} = 1.0 μM; 5-LOX IC_{50} = 3.2 μM; 15-LOX IC_{50} = 3.2 μM). Compound **13c** exhibited LOX inhibitory activity comparable to the reference drugs caffeic acid (5-LOX IC_{50} = 3.0 μM) and luteolin (15-LOX IC_{50} = 3.2 μM), respectively. A further increase in alkyl chain length from *n*-Pr to *n*-Bu (**13d**, R^2 = *n*-Bu), provided a gain in both COX-2 (COX-1 IC_{50} > 100 μM; COX-2 IC_{50} = 10.0 μM; SI > 10) and 5-LOX (5-LOX IC_{50} = 4.5 μM; 15-LOX IC_{50} > 10 μM) selectivity albeit with a loss in COX-2 and 5-LOX inhibitory potency compared to **13c**. It is notable that introduction of an *i*-Pr substituent at the para-position of the C-1 phenyl ring (**13e**, R^2 = *i*-Pr) provided dual inhibition of both COX and LOX enzymes. Compound **13e** exhibited moderate COX-2 selectivity (COX-1 IC_{50} = 9.2 μM; COX-2 IC_{50} = 0.32 μM; SI = 28) and an equipotent inhibition of 5/15-LOX (5-LOX IC_{50} = 0.32 μM; 15-LOX IC_{50} = 0.36 μM). Compound **13e** was a 1.5-fold more potent inhibitor of COX-2 than the reference drug rofecoxib (COX-2 IC_{50} = 0.50 μM), and it was a 9-fold more potent inhibitor of both 5 and 15-LOX compared to the reference drugs caffeic acid (5-LOX IC_{50} = 3.0 μM) and luteolin (15-

Table 1. COX-1/2 and 5/15-LOX Inhibitory Activities of the 1,3-Diarylprop-2-yn-1-ones (**13a**−**p**, **17a**−**c**, **23a**,**b**, **26a**−**c**, **27** and **28**)



Cmpd	R^1	R^2	R^3	IC_{50} (μM) [a] COX-1	IC_{50} (μM) [a] COX-2	Selectivity [b] Index (S.I.)	IC_{50} (μM) [a] 5-LOX	IC_{50} (μM) [a] 15-LOX	Volume (Å^3) [c]
13a	H	H	H	1.0	10.0	–	> 10	> 10	245.7
13b	H	Me	H	> 100	33.0	> 3.3	> 10	> 10	262.3
13c	H	*n*-Pr	H	3.2	1.0	3.2	3.2	3.2	295.4
13d	H	*n*-Bu	H	> 100	10.0	> 10.0	4.5	> 10	312.0
13e	H	*i*-Pr	H	9.2	0.32	28.0	0.32	0.36	295.2
13f	H	CF_3	H	3.1	> 100	–	> 10	> 10	275.0
13g	H	CN	H	31.5	1.0	31.5	1.0	3.2	263.1
13h	H	F	H	30.0	0.10	300	> 10	1.0	250.3
13i	F	F	H	3.1	0.50	6.2	0.40	3.2	254.3
13j	H	OMe	H	31.5	31.5	1.0	> 10	3.5	271.0
13k	H	OH	H	3.5	10.0	–	0.30	0.32	254.2
13l	OMe	H	H	> 100	10.0	> 10.0	9.0	> 10	271.0
13m	OH	H	H	> 100	> 100	–	0.30	0.50	254.2
13n	OMe	OMe	H	3.3	> 100	–	1.0	> 10	296.2
13o	OMe	OMe	OMe	> 100	> 100	–	7.0	> 10	321.7
13p	H	COOMe	H	> 100	0.54	> 185	> 10	5.0	290.0
17a		–	–	1.0	> 100	–	0.1	> 10	228.3
17b		–	–	> 100	2.6	> 38	> 10	> 10	289.9
17c		–	–	> 100	0.60	> 166	> 10	0.30	314.6
23a	OMe	OH	H	1.1	30.0	–	> 10	0.10	278.7
23b	OH	OMe	H	1.0	3.2	–	> 10	0.30	278.7
26a		–	–	32.2	10.0	3.2	1.5	> 10	224.2
26b	H	NO_2	H	0.25	31.6	–	6.2	> 10	268.5
26c	NO_2	H	H	2.0	3.0	–	> 10	3.5	268.5
27	H	SMe	H	9.2	0.32	28.0	0.32	0.36	280.3
28	–	–	–	> 100	> 100	–	> 10	> 10	289.0
Luteolin	–	–	–	–	–	–	–	3.2	231.9
Caffeic acid	–	–	–	–	–	–	3.0	–	153.5
NDGA	–	–	–	–	–	–	> 10	3.5	285.3
Aspirin	–	–	–	0.35	2.4	–	–	–	154.8
Rofecoxib	–	–	–	> 100	0.50	> 200	–	–	267.2
Celecoxib	–	–	–	33.1	0.07	474	–	–	298.5

[a] Values are means of two determinations and deviation from the mean is <10% of the mean value (Catalog No. 560101, 760700 and 60401 Cayman Chemicals Inc., Ann Arbor, MI). [b] In vitro COX-2 selectivity index (IC_{50} COX-1/IC_{50} COX-2). [c] The volume of the molecule after minimization using the PM3 force field was calculated using the Alchemy 2000 program.

LOX IC_{50} = 3.2 μM). In contrast **13f**, possessing a C-1 *p*-CF_3-phenyl moiety (R^2 = CF_3), exhibited COX-1 selectivity (COX-1 IC_{50} = 3.1 μM; COX-2 IC_{50} > 100 μM).

It is also of interest that introduction of a C-1 *p*-CN-phenyl ring (**13g**, R^2 = CN) provided dual COX (COX-2 IC_{50} = 1.0 μM; COX-1 IC_{50} = 31.5 μM) and LOX inhibition with moderate COX-2 selectivity (SI = 31.5). In addition, **13g** exhibited a more potent inhibition of 5-LOX (5-LOX IC_{50} = 1.0 μM) compared to 15- LOX (15-LOX IC_{50} = 3.2 μM) as shown in Table 1. Within this class of compounds, **13h** possessing a C-1 *p*-

fluorophenyl substituent, was a potent and selective inhibitor of COX-2 (COX-2 $IC_{50} = 0.1\ \mu M$; SI = 300), being 5-fold more potent than rofecoxib (COX-2 $IC_{50} = 0.5\ \mu M$; SI > 200) although it was less potent than celecoxib (COX-2 $IC_{50} = 0.07\ \mu M$; SI = 474). On the other hand, introduction of a C-1 3,4-difluorophenyl substituent (**13i**, $R^1 = R^2 = F$) decreased both COX-2 inhibitory potency and selectivity (COX-2 $IC_{50} = 0.5\ \mu M$; SI = 6.0) but provided a gain in 5-LOX inhibition (5-LOX $IC_{50} = 0.4\ \mu M$). Incorporating a C-1 *p*-MeO-phenyl substituent (**13j** provided weak COX but potent 15-LOX inhibition (COX-1/2 $IC_{50} = 31.5\ \mu M$; 15-LOX $IC_{50} = 3.5\ \mu M$), whereas incorporation of a *p*-SMe substituent (**27**, R^2 = SMe) resulted in a large increase in COX-2 inhibitory potency and selectivity (COX-2 $IC_{50} = 0.32\ \mu M$; SI = 28), 5-LOX ($IC_{50} = 0.32\ \mu M$) and 15-LOX ($IC_{50} = 0.36\ \mu M$) inhibitions. In contrast, incorporation of a *p*-SO_2Me substituent on both the C-1 and C-2 phenyl ring (**28**) led to a complete loss in both COX and LOX inhibitory activity. Introduction of a C-1 *m*-MeO-phenyl substituent (**13l**) increased both COX-2 inhibitory potency and selectivity (COX-2 $IC_{50} = 10\ \mu M$; SI > 10) with a moderate gain in 5-LOX (5-LOX $IC_{50} = 9.0\ \mu M$) inhibition compared to the regioisomer **13j**. On the other hand, introduction of a 3,4-dimethoxyphenyl group (**13n**, $R^1 = R^2$ = OMe) provided a gain in both COX-1 (COX-1 $IC_{50} = 3.3\ \mu M$) and 5-LOX (5-LOX $IC_{50} = 1.0\ \mu M$) inhibitory potency and selectivity. However, incorporation of a C-1 3,4,5-trimethoxyphenyl moiety (**13o**, $R^1 = R^2 = R^3$= OMe) resulted in a complete loss of COX inhibitory activity, but **13o** did exhibit selective inhibition of 5-LOX (5-LOX $IC_{50} = 7.0\ \mu M$) albeit was less potent than compared to **13n**. Within this sub group of C-1 methoxy substituted compounds (**13j**, **13l**, **13n** and **13o**) the COX-2 potency order was 3-OMe > 4-OMe > inactive 3,4-di-OMe and 3,4,5-tri-OMe, and the 5-LOX potency order was 3,4-di-OMe > 3,4,5-tri-OMe > 3-OMe > inactive 4-OMe. The potency order for 15-LOX was 4-OMe > inactive 3-OMe, 3,4-di-OMe_2 and 3,4,5-tri-OMe_3. The C-1 4-hydroxyphenyl compound (**13k** R^2 = OH) exhibited dual inhibition of COX and LOX. However, **13k** was not a potent inhibitor of either COX-1 (COX-1 $IC_{50} = 3.5\ \mu M$) or COX-2 (COX-2 $IC_{50} = 10.0\ \mu M$). On the other hand, **13k** exhibited equipotent inhibition of both 5- and 15-LOX (5-LOX $IC_{50} = 0.3\ \mu M$; 15-LOX $IC_{50} = 0.32\ \mu M$), and it was a 9-fold more potent inhibitor of 5-LOX than the reference drug caffeic acid (5-LOX $IC_{50} = 3.0\ \mu M$). In contrast, introduction of a hydroxy substituent at the meta-position of the C-1 phenyl ring (**13m**, R^1 = OH) led to a complete abolition of COX inhibitory potency (COX-1/2 $IC_{50} > 100\ \mu M$) while retaining 5/15-LOX inhibitory potency (5-LOX $IC_{50} = 0.3\ \mu M$; 15-LOX $IC_{50} = 0.5\ \mu M$). Introduction of a methoxyphenol moiety at the C-1 position provided compounds **23a** (R^1 = OMe, R^2 = OH) and **23b** (R^1 = OH, R^2 = OMe) that exhibited moderate COX-1 selectivity, with preferential inhibition of 15-LOX (Table 1). Compound **23a**, which is a potent inhibitor of 15-LOX (15-LOX $IC_{50} = 0.1\ \mu M$), is 35-fold more potent than the reference drug nordihydroguiarectic acid (NDGA, 15-LOX $IC_{50} = 3.5\ \mu M$).

It was interesting to note that introduction of an electron withdrawing group at the para-position of the C-1 phenyl ring (**13p**, $R^2 = COOCH_3$) provided dual inhibition of COX-2 and 15-LOX (15-LOX $IC_{50} = 5.0\ \mu M$). Compound **13p** exhibited good COX-2 inhibitory potency and selectivity (COX-2 $IC_{50} = 0.54\ \mu M$; COX-1 $IC_{50} > 100\ \mu M$; SI > 185) and was an equipotent inhibitor compared to the reference drug rofecoxib (COX-2 $IC_{50} = 0.50\ \mu M$; SI > 200). In contrast, introduction of an electron withdrawing group such as a nitro substituent at the C-1 *meta* or para-position provided compounds (**26b**, $R^2 = NO_2$; **26c**, $R^1 = NO_2$) that showed contrasting LOX inhibitory activities with compound **26b** ($R^2 = NO_2$) exhibiting 5-LOX selectivity (5-LOX $IC_{50} = 6.2\ \mu M$), whereas **26c** exhibited 15-LOX selectivity (5-LOX $IC_{50} = 3.5\ \mu M$) as shown in Table 1.

Incorporation of a naphthyl substituent at the C-1 position (**17b**) provided a COX-2 selective compound although **17b** (COX-2 $IC_{50} = 2.6\ \mu M$; COX-1 $IC_{50} > 100\ \mu M$; SI > 38), was not as potent as the reference drug rofecoxib, and it did not inhibit 5/15-LOX up to a concentration of 10 μM (see data in Table 1). However, introduction of a methoxy substituent at the 4-position of the naphthyl ring (**17c**) led to a dramatic gain in both COX-2 (COX-2 $IC_{50} = 0.6\ \mu M$; COX-1 $IC_{50} > 100\ \mu M$; SI > 166) and 15-LOX (5-LOX $IC_{50} > 10\ \mu M$; 15-LOX $IC_{50} = 0.3\ \mu M$) inhibitory potency. Introduction of a heterocyclic furanyl ring at the C-1 position (**17a**), provided a COX-1 and 5-LOX selective compound. Compound **17a** was a 30-fold more potent inhibitor of 5-LOX ($IC_{50} = 0.1\ \mu M$) than the reference drug caffeic acid (5-LOX $IC_{50} = 3.0\ \mu M$). In contrast, introduction of an isoxazole ring at the C-1 position (**26a**) provided a moderate gain in COX-2 selectivity (COX-2 $IC_{50} = 10.0\ \mu M$; COX-1 $IC_{50} = 32.3\ \mu M$; SI = 3.2) while retaining 5-LOX selectivity ($IC_{50} = 1.5\ \mu M$) even though it was less potent compared to **17a**.

The in vitro data acquired for this class of 1,3-diarylprop-2-yn-1-ones (**13a**−**p**, **17a**−**c**, **23a**,**b**, **26a**−**c**, **27** and **28**) show that COX and LOX inhibition can be manipulated by varying the electronic and steric properties of substituents attached to the C-1 phenyl ring. For example, compounds possessing an *n*-Pr, *i*-Pr, CN, 3,4-di-F_2 or *p*-OH substituents at the para-position of the C-1 phenyl ring (**13c**, **13e**, **13g**, **13j** and **13k**) exhibited dual inhibition of both COX-1/2 and 5/15-LOX enzymes. The COX-2 inhibitory potency order for these compounds was *p*-F > *p*-*i*-Pr > 3,4-di-F_2 > *p*-COOMe > 4-MeO-naphthyl > *p*-*n*-Pr ≈ *p*-CN > naphthyl ≈ *m*-NO_2 > *p*-OH ≈ *m*-OMe ≈ *p*-SMe ≈ isoxazole, whereas the 5-LOX inhibitory potency was of the order furanyl > *m*-OH ≈ *p*-OH ≈ *i*-Pr > 3,4-di-F_2 > *p*-CN ≈ 3,4-di-OMe_2 > isoxazole > *n*-Bu > *p*-NO_2 > 3,4,5-tri-OMe_3 > *m*-OMe. It is interesting to note that compounds possessing a hydroxyl substituent on the C-1 phenyl ring (**13k**, **13m**, **23a** and **23b**) generally exhibited potent inhibition of 15-LOX suggesting that these compounds could act as antioxidants. The 15-LOX inhibitory potency was of the order 3-OMe-4-OH > 3-OH-4-MeO > 4-OMe-naphthyl > *p*-OH > *i*-Pr > *m*-OH > *p*-SMe > *p*-CN ≈ m-NO_2 ≈ *p*-OMe > *p*-COOMe.

The critical difference between the binding sites for COX-1 and COX-2 is at position 523 where COX-2 has a smaller Val residue in place of the bulkier Ile in COX-1. This difference produces a secondary pocket extending off the primary binding site in COX-2 that is absent in COX-1. Consequently, the combined volume of the primary binding site and the secondary pocket in COX-2 is about 25% larger (394 $Å^3$) than the volume of the COX-1 binding site (316 $Å^3$).[24] This group of 1,3-diarylprop-2-yn-1-ones (**13a**−**p**, **17a**−**c**, **23a**,**b**, **26a**−**c**, **27** and **28**) possess a wide range of molecular volumes (224.2−321.7 $Å^3$). Compounds exhibiting COX-2 selectivity have volumes in the range of 290−314.6 $Å^3$ with the exception of compound **13h** (R^2 = F) that has a volume of 250.3 $Å^3$. It is known that the various LOX isoforms also differ in their binding site volumes. For example, the volume of the 5-LOX binding site (470 $Å^3$) is much larger than that of 15-LOX (390 $Å^3$).[25] In this study, compounds exhibiting 5-LOX inhibitory potency have molecular volumes in the range of 253.8.-321.7 $Å^3$, with the exception of compounds possessing a C-1 heterocyclic sub-

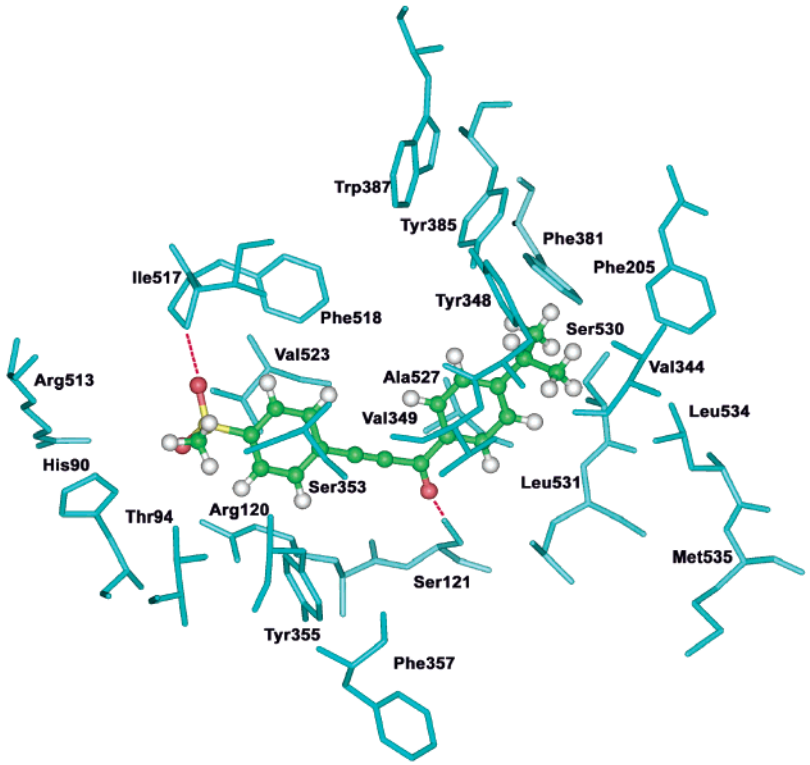


Figure 1. Docking 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**) (ball-and-stick) in the active site of murine COX-2 ($E_{intermolecular}$ = −63.17 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

stituent (**17a** = 228.3 Å^3 and **26a** = 224.2 Å^3), that are only marginally larger than compounds exhibiting 15-LOX inhibitory potency with molecular volumes in the range of 253.8−314.6 Å^3.

Molecular modeling (docking) studies were carried out to investigate the binding interactions of certain 1,3-diphenylprop-2-yn-1-ones within the COX and LOX binding sites. The binding interaction of 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**, COX-2 IC_{50} = 0.32 μM; SI = 28) within the COX-2 binding site is illustrated in Figure 1. The most stable enzyme−ligand complex shows that the C-3 *p*-$MeSO_2$-phenyl moiety is oriented within the vicinity of the COX-2 secondary pocket where it undergoes interaction with the amino acid residues Val523, Phe518, Ile517, Ser353, Leu352 and His90. The distance between the center of C-3 *p*-$MeSO_2$-phenyl ring and that of Phe518 is about 6.53 Å. One of the oxygen atoms of SO_2Me undergoes a hydrogen bonding interaction with the backbone N*H* of Ile517 (distance = 3.33 Å), and it is positioned about 4.27 Å from the NH_2 of Arg513. The other *O*-atom of the SO_2Me substituent is about 5.23 Å away from the backbone N*H* of Phe518. The methyl group of SO_2Me, located in the vicinity of Ala516, Thr94 and Ser353, is about 3.96 Å from the methyl side chain of Thr94. It is interesting to note that the C=*O* of the central prop-2-yn-1-one (C≡C−C=O) participates in a favorable hydrogen bonding interaction with the O*H* of Ser121 closer to the mouth of the COX-2 binding site (distance = 2.66 Å). In this regard, in a previous study the most potent and selective COX-2 inhibitor **13h** (R^2 = F) interacted favorably with Tyr355 closer to the mouth of the COX-2 binding site.[16] The C-1 *p*-*i*-Pr-phenyl substituent is oriented toward the apex of the COX-2 active site in the vicinity of the amino acid residues Ser530, Leu531, Tyr385, Tyr348 and Phe381. The *p*-isopropyl substituent is positioned in the vicinity of a hydrophobic pocket where it is

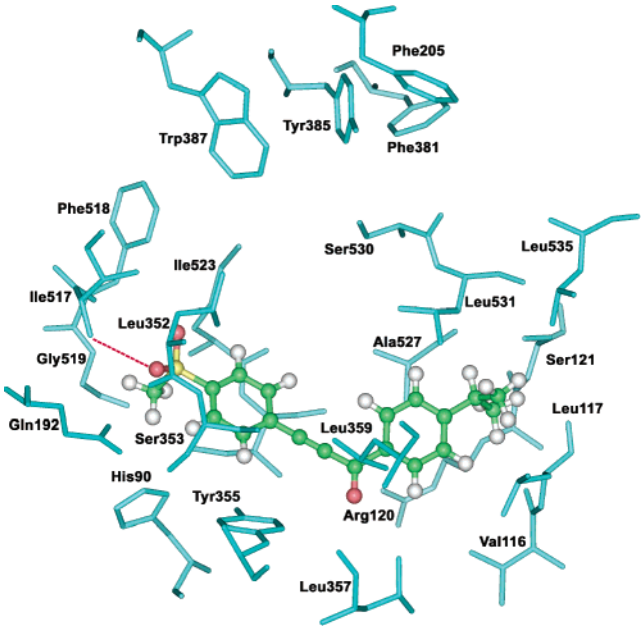


Figure 2. Docking 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**) (ball-and-stick) in the active site of ovine COX-1 ($E_{intermolecular}$ = −59.14 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

within van der Waals contact range of the amino acid residues Phe205, Val344, Val349, Phe381 and Leu534 (distance < 5 Å).

A similar docking study for **13e** (COX-1 IC_{50} = 9.2 μM) was carried out within the COX-1 binding site which shows it binds in an extended conformation (see Figure 2). It is interesting to note that the C-3 phenyl ring possessing the *p*-SO_2Me COX-2 pharmacophore is located in the side pocket, facing Ile517 and that one of the *O*-atoms of SO_2Me substituent undergoes a favorable hydrogen bonding interaction with the backbone N*H*

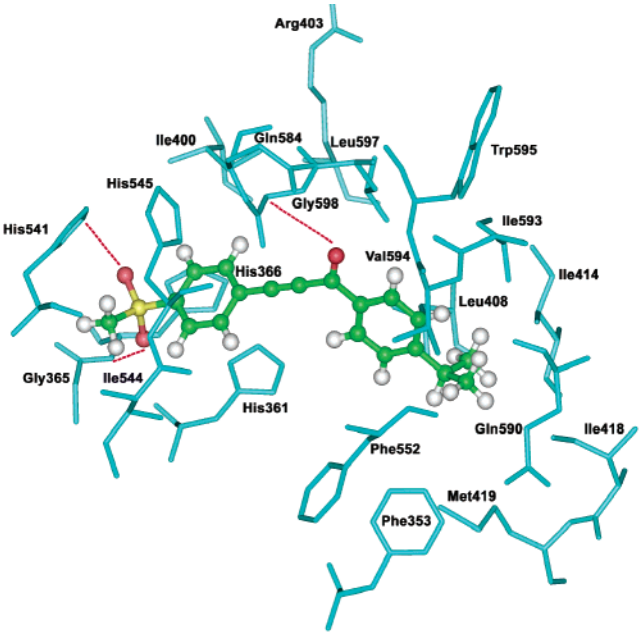


Figure 3. Docking 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**) (ball-and-stick) in the active site of rabbit 15-LOX ($E_{intermolecular}$ = −54.41 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

of Ile517 (distance = 2.15 Å). The C=*O* of the central prop-2-yn-1-one (C≡C−C=O) that, in contrast to COX-2, does not participate in hydrogen bonding with Ser121, and it is far removed from either Tyr355 or Arg120 present at the mouth of the COX-1 binding site. It was also observed that the C-1 *i*-Pr-phenyl ring is oriented toward a hydrophobic pocket close to the mouth of the COX-1 binding site, and that it is not oriented toward the apex of the COX-1 binding site as for the interaction of **13e** within COX-2 binding site. The C-1 *p*-*i*-Pr substituent is within van der Waals contact range of hydrophobic amino acid residues such as Val116, Leu117, Leu357 (Phe357 in COX-2) and Leu535 (Met535 in COX-2) (distance < 5 Å). These observations suggests that the steric hindrance arising from the presence of a bulkier Ile523 is not enough to prevent binding of **13e** within the COX-1 binding site.

The most stable enzyme−ligand complex for **13e** (15-LOX IC_{50} = 0.36 μM) within the 15-LOX binding site is shown in Figure 3. The substrate binding site for mammalian 15-LOX is a boot shaped cavity (volume = 390 Å^3)[25] with the hydrophobic amino acid residues Phe353, Ile418, Met419 and Ile593 located at the base of the binding site. A charged Arg403 is present at the mouth of (opening to) the binding site. It is of interest that the linear C≡C (of the central C≡C−C=O) of **13e** orients the C-3 *p*-SO_2Me-phenyl moiety toward a region that is closer to the catalytic iron site (His361, Gly365, His366, Ile400, His541, Ile544 and His545). The His361 is positioned directly behind the plane of C-3 *p*-$MeSO_2$-phenyl moiety with which it undergoes a $\pi-\pi$ interaction. One of the *O*-atoms of the *p*-SO_2-Me COX-2 pharmacophore forms a hydrogen bond with the N*H* of His541 (distance = 3.43 Å) while the other *O*-atom forms a hydrogen bond with the backbone N*H* of His366 (distance = 2.78 Å). The Me of the SO_2Me moiety is within van der Waals contact range of Gly365 and Ile544 (distance < 5 Å). The C=*O* of the central C≡C−C=O undergoes a hydrogen bonding interaction with the backbone N*H* of Gly598 (distance = 2.03 Å) closer to the entrance of the 15-LOX binding site, and the distance between the charged NH_2 (guanidino group) of Arg403 and C=*O* is about 13.22 Å. The C-1 *p*-*i*-Pr-phenyl substituent is buried deep inside a hydrophobic pocket at the base of 15-LOX binding site. The *p*-*i*-Pr group is positioned such that it can undergo van der Waals interactions with the amino acid residues Ile414, Ile418, Met419 and Ile593 (distance < 5 Å).

A similar docking experiment to determine the binding interaction of 3-(4-methanesulfonylphenyl)-1-(4-hydroxy-3-

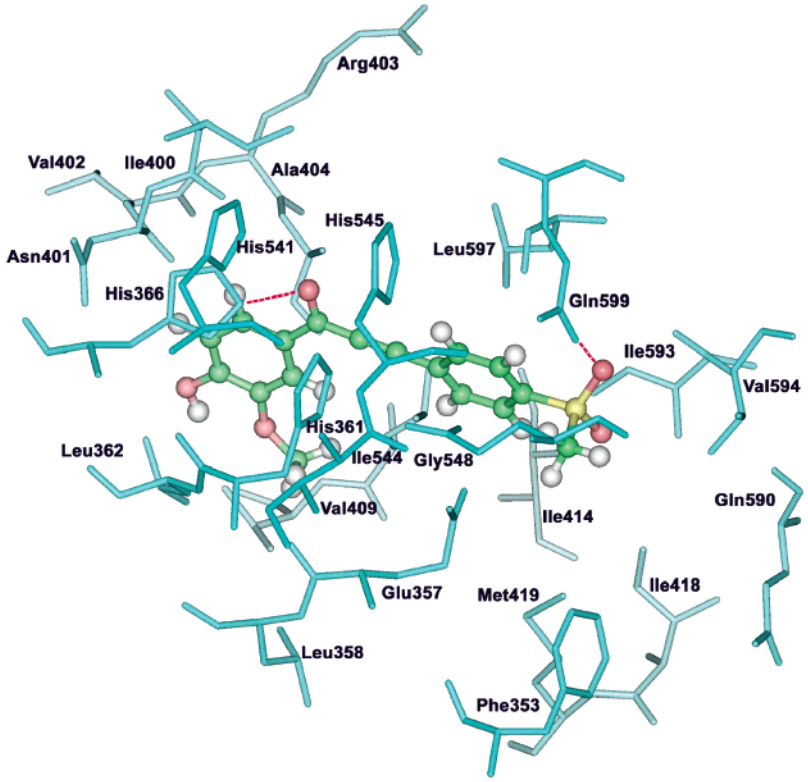


Figure 4. Docking 3-(4-methanesulfonylphenyl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-yn-1-one (**23a**) (ball-and-stick) in the active site of rabbit 15-LOX ($E_{intermolecular}$ = −63.57 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

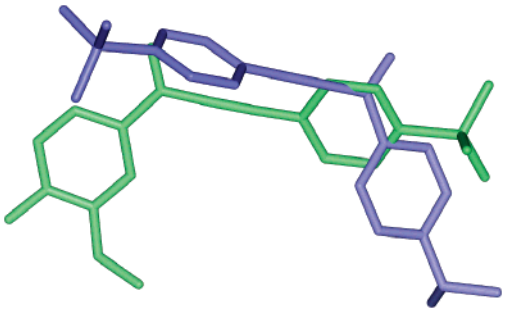
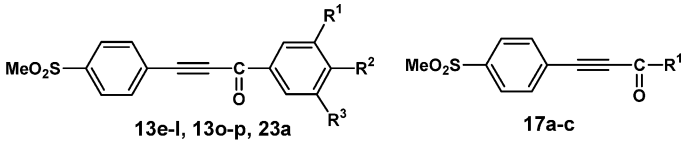
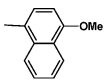


Figure 5. Over lay of the binding modes of 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**, blue) and 3-(4-methanesulfonylphenyl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-yn-1-one (**23a**, green) in the active sites of 15-LOX. Hydrogen atoms are not shown for clarity.

methoxyphenyl)prop-2-yn-1-one (**23a**, 15-LOX $IC_{50} = 0.1\ \mu M$) within the 15-LOX binding site indicates a different picture compared to that of **13e** (Figure 4 and Figure 5). In this regard, compound **23a** is oriented in a reverse conformation where the C-3 *p*-SO_2Me-phenyl moiety is oriented toward the base of the active site, and the C-1 methoxyphenol terminus of the molecule is located near the catalytic iron (Figure 4). The *p*-SO_2Me COX-2 pharmacophore is positioned within van der Waals contact range (<5 Å) of the amino acid residues Ile418, Met419, Leu597 and Ile593. It is noteworthy that one of the oxygen-atoms of the *p*-SO_2Me substituent forms a hydrogen bond with the N*H*$_2$ of Gln599 (distance = 2.40 Å). The linear C≡C is surrounded by Gln357 and Ala404, whereas the C=*O* of the central prop-2-yn-1-one (C≡C−C=O) is oriented toward the catalytic iron where it interacts with His361, His366 and Ala404. The C=*O* of prop-2-yn-1-one forms a hydrogen bond with the N*H* of His366 (distance = 2.74 Å). The C=*O* is much closer to the N*H*$_2$ (guanidino) group of Arg403 (distance = 8.86 Å) located at the opening of the 15-LOX binding site compared to **13e**. The C-1 methoxyphenol substituent is oriented in the direction of the catalytic iron site where it is positioned in a region comprised of the hydrophobic amino acid residues Leu362, Ile400, Val402, Ala 404 and Val409. The C-1 3-OMe substituent is within van der Waals contact range of the amino acid residues Ala404, Leu408 and Val409 (distance < 5 Å). The C-1 4-O*H* substituent can interact with Leu362, Ile385 and the polar Asn401. The distance between the C-1 4-O*H* substituent and the *N*H$_2$ of Asn401 is about 4.81 Å. It should be noted that **13e** and **23a** possessing a C-3 *p*-SO_2Me COX-2 pharmacophore display contrasting binding conformations within

Table 2. Antiinflammatory and Analgesic Activities of the 1,3-Diarylprop-2-yn-1-ones (**13e**−**l**, **13o**,**p**, **17a**−**c** and **23a**)



Cmpd	R^1	R^2	R^3	AI Activity [a] % Inhibition at 3 hours	AI Activity [a] ED_{50} mg/kg	Analgesic Activity [b] % Inhibition at 30 min	Analgesic Activity [b] % Inhibition at 60 min
13e	H	*i*-Pr	H	48.1 ± 3.1	35.0	40.7 ± 14.0	53.7 ± 07.5
13f	H	CF_3	H	16.2 ± 2.5	–	38.0 ± 03.4	66.2 ± 06.3
13g	H	CN	H	29.6 ± 3.6	90.0	48.6 ± 12.1	36.2 ± 05.1
13h	H	F	H	26.3 ± 2.0	–	83.8 ± 04.5	72.0 ± 10.0
13i	F	F	H	06.8 ± 1.7	–	50.8 ± 11.7	46.1 ± 09.7
13j	H	OMe	H	30.2 ± 1.7	60.1	42.7 ± 06.6	38.6 ± 03.7
13k	H	OH	H	37.4 ± 5.0	51.3	52.4 ± 07.0	56.6 ± 06.2
13l	OMe	H	H	24.2 ± 4.1	–	72.6 ± 07.0	54.7 ± 07.5
13o	OMe	OMe	OMe	35.7 ± 7.2	112.8	60.2 ± 12.0	46.2 ± 05.2
13p	H	COOMe	H	21.5 ± 1.0	–	56.2 ± 08.6	71.2 ± 08.3
17a		–	–	26.4 ± 3.5	–	57.7 ± 10.8	76.6 ± 06.2
17b		–	–	08.8 ± 0.6	–	56.4 ± 10.0	40.3 ± 08.6
17c		–	–	24.0 ± 3.6	–	56.7 ± 10.8	36.7 ± 04.7
23a	OMe	OH	H	26.0 ± 0.7	–	15.4 ± 12.1	45.8 ± 15.2
Caffeic acid	–	–	–	08.2 ± 2.5	–	47.2 ± 10.6	58.3 ± 12.8
NDGA	–	–	–	15.1 ± 1.7	205.0	45.8 ± 09.2	62.5 ± 04.8
Aspirin	–	–	–	–	129.0	29.7 ± 10.7	46.4 ± 14.1
Celecoxib	–	–	–	–	10.8	69.3 ± 12.1[c]	79.5 ± 02.0[c]

[a] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as mean ± SEM ($n = 4-6$) following a 30 mg/kg oral dose of the test compound or as the ED_{50} values when it was determined. [b] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as mean ± SEM ($n = 4-6$) following a 30 mg/kg oral dose of the test compound. [c] 5 mg/kg oral dose.

the 15-LOX binding site, suggesting that the electronic and steric properties at the C-1 phenyl ring also contributes to the binding of these ligands to 15-LOX (Figure 5).

In vivo pharmacological studies were carried out to evaluate the antiinflammatory and analgesic activity potential for the 1,3-diarylprop-2-yn-1-ones (**13e**−**l**, **13o**−**p**, **17a**−**c** and **23a**) and the results are listed in Table 2. In a rat carrageenan-induced paw edema assay these 1,3-diarylprop-2-yn-1-ones exhibited weak to good antiinflammatory activities (6.8−48% inhibition of inflammation) at 3 h after administration for a 30 mg/kg oral dose. The dual COX-1/2 and 5/15-LOX inhibitor compound 3-(4-methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (**13e**, COX-1 IC_{50} = 9.2 μM; COX-2 IC_{50} = 0.32 μM; SI = 28; 5-LOX IC_{50} = 0.32 μM; 15-LOX IC_{50} = 0.36 μM) was the most potent antiinflammatory agent in this series exhibiting 48% inhibition of inflammation at 3 h after administration of a 30 mg/kg oral dose. Compound **13e** is about 5.8-fold and 3.2-fold more potent than the respective reference drugs nordihydroguiaretic acid (NDGA) and caffeic acid (15 and 8% inhibition of inflammation for a 30 mg/kg oral dose). However, **13e** was not as potent (ED_{50} = 35 mg/kg) as the reference drug celecoxib (10.8 mg/kg) as an antiinflammatory agent. Accordingly, the dual COX-1/2 and 5/15-LOX inhibitor 3-(4-methanesulfonylphenyl)-1-(4-cyanophenyl)prop-2-yn-1-one (**13g**, COX-1 IC_{50} = 31.5 μM; COX-2 IC_{50} = 1.0 μM; SI = 31.5; 5-LOX IC_{50} = 1.0 μM; 15-LOX IC_{50} = 3.2 μM) exhibited respectable antiinflammatory activity (ED_{50} = 90 mg/kg) since it is more potent than the reference drug aspirin (ED_{50} = 129 mg/kg). The most potent and selective COX-2 inhibitor 3-(4-methanesulfonylphenyl)-1-(4-fluorophenyl)prop-2-yn-1-one (**13h**, COX-2 IC_{50} = 0.1 μM; SI > 300) exhibited moderate antiinflammatory activity (26% inhibition of inflammation) at 3 h after administration of a 30 mg/kg oral dose. The selective 5-LOX inhibitor **13o** ($R^1 = R^2 = R^3$ = OMe) exhibited good antiinflammatory activity (ED_{50} = 112.8 mg/kg) since it is about 1.8-fold more potent than the reference drug NDGA (ED_{50} = 205 mg/kg). In this regard, the most potent 15-LOX inhibitor 3-(4-methanesulfonylphenyl)-1-(4-hydroxy-3-methoxyphenyl)-prop-2-yn-1-one (**23a**, 15-LOX IC_{50} = 0.1 μM) exhibited a 26% inhibition of inflammation at 3 h after administration of a 30 mg/kg oral dose. Further studies are required to determine the most ideal COX-2/COX-1 and/or 5-LOX/15-LOX values. The in vivo antiinflammatory data for compounds **13** (see Table 2) appear to suggest that compounds showing the most potent inhibition of both 5-LOX and 15-LOX in conjunction with nonselective inhibition of the COX isozymes are among the most potent antiinflammatory agents in this group of 1,3-diarylprop-2-yn-1-ones.

In vivo analgesic activity was determined using the rat 4% NaCl-induced abdominal constriction assay. These compounds (**13e**−**l**, **13o**−**p**, **17a**−**c** and **23a)** exhibited moderate to good analgesic activities (36−84% inhibition of writhing) at different time intervals after administration of a 30 mg/kg oral dose. Among this series of compounds **13i** ($R^1 = R^2$ = F, R^3 = H) exhibited excellent analgesic activity where a 30 mg/kg oral dose reduced writhing by 84 and 72% at 30 and 60 min postdrug administration since it showed superior analgesic activity compared to the reference drug NDGA (46 and 62.5% inhibition of writhing at 30 and 60 min postdrug administration). The most potent antiinflammatory agent **13e** exhibited 41 and 54% inhibition of writhing at 30 and 60 min postdrug administration (30 mg/kg oral dose).

Conclusions

The strucureactivity relationship (SAR) data acquired show that (i) the 1,3-diarylprop-2-yn-1-one structure is a suitable template to design dual inhibitors of COX and LOX; (ii) COX-2 selectivity requires a *p*-SO_2Me COX-2 pharmacophore on the C-3 phenyl ring; (iii) optimal dual COX-1/2 and 5/15-LOX inhibition can be achieved by varying the electronic and steric properties at the C-1 phenyl ring substitution pattern (eg: **13e**, R^2 = *i*-Pr; **13g**, R^2 = CN); (iv) molecular modeling studies show, for this class of compounds, that the C-3 *p*-SO_2Me COX-2 pharmacophore can adopt contrasting binding modes within the 15-LOX binding site; (v) dual inhibitors of both COX-1/2 and 5/15-LOX possess clinically relevant oral antiinflammatory and analgesic activities (eg: **13e**, R^2 = *i*-Pr; **13g**, R^2 = CN).

Experimental Section

General. Melting points were determined using a Buchi capillary apparatus and are uncorrected. All other reagents were purchased from Aldrich (Milwaukee, WI). Silica gel column chromatography was performed using Merck silica gel 60 ASTM (70−230 mesh). Infrared (IR) spectra were recorded using a Nicolet 550 Series II Magna FT-IR spectrometer. Nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker AM-300 spectrometer and chemical shifts are expressed in parts per million (ppm, δ) relative to tetramethylsilane as internal standard. Spin multiplets are given as s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet) and m (multiplet). Coupling constants (*J*) are given in Hertz (Hz). Microanalyses were performed for C, H and N (Micro Analytical Service Laboratory, Department of Chemistry, University of Alberta) and were within ± 0.4% of the theoretical values. Celecoxib and rofecoxib were synthesized according to the literature procedures.[1,26] Luteolin, caffeic acid and nordihydroguaiaretic acid (NDGA) were purchased from Cayman Chemicals Inc. Ann Arbor, MI. Acetyl salicylic acid (aspirin) was purchased from Sigma Chemical Company. 3-(4-Methylsulfanylphenyl)-1-phenylprop-2-yn-1-ol (**11a**) and other derivatives possessing a C-1 *p*-Me, OMe, F or CF_3 substituent (compounds **11b**−**e**) and 3-(4-methylsulfanylphenyl)-1-phenylprop-2-yn-1-one (**12a**) and other derivatives possessing a C-1 *p*-Me, OMe, F or CF_3 substituent (compounds **12b**−**e**), 3-(4-methanesulfonylphenyl)-1-phenylprop-2-yn-1-one (**13a**) and 3-(4-methanesulfonylphenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-one (**27**) were prepared according to a previously reported method.[20] Male Sprague−Dawley rats, used in the antiinflammatory 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.

2-Methyl-4-(4-methylsulfanylphenyl)but-3-yn-2-ol (8). 4-Bromothioanisole (**7**, 49.2 mmol) was added slowly under an argon atmosphere to a stirred solution of freshly dried EtN_3 (100 mL, 730.6 mmol) at 25 °C. To this solution, $PdCl_2(PPh_3)_2$ (0.14 g, 0.19 mmol), 2-methyl-3-butyn-2-ol (5.06 mL, 52.1 mmol) and CuI (40 mg, 0.21 mmol) were added successively, and the reaction mixture was refluxed under an argon atmosphere for 6 h at 70−75 °C. The cooled reaction mixture was filtered and excess TEA was evaporated in vacuo to furnish a dark brown mixture that was purified by silica gel column chromatography using hexanes−ethyl acetate (3:1, v/v) as eluent to afford **8** as a pale yellow solid (75%, 7.6 g). mp 70−72 °C; IR (film): 3655 (OH), 2130 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.61 [s, 6H, C(CH_3)$_2$], 2.01 (br s, 1H, O*H*), 2.48 (s, 3H, SCH_3), 7.14 (d, *J* = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.30 (d, *J* = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6).

1-Ethynyl-4-methylsulfanylbenzene (9). 2-Methyl-4-(4-methylsulfanylphenyl)but-3-yn-2-ol (**8**, 48.5 mmol) was dissolved in benzene (40 mL), NaH (0.16 g, 6.45 mmol) was added, and the reaction mixture was heated at 105−110 °C for 1 h. Removal of the solvent in vacuo gave a dark brown oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (3:1, v/v) as eluent to afford **9** as a yellowish brown oil (55%, 3.9 g).

IR (film): 2112 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.49 (s, 3H, SC*H*$_3$), 3.07 (s, 1H, −C≡C*H*), 7.16 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.39 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6).

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ols (11 and 15a−c). 1-Ethynyl-4-methylsulfanylbenzene (**9**, 9.75 mmol) was added slowly under an argon atmosphere to a stirred solution of freshly dried THF (10 mL) at −78 °C. A solution of *n*-BuLi (4 mL of 2.5 M in hexane) was added slowly. After 3 min a solution of the respective substituted-benzaldehyde (**10**, R^1 = H, OMe, F, NO_2; R^2 = H, OMe, F, NO_2, CN, *n*-Pr, *n*-Bu, *i*-Pr, COOMe; R^3 = H, OMe or **14a−c** (R^1 = furanyl, naphthyl or methoxynaphthyl; 9.75 mmol) in dry THF (5 mL) was added slowly while maintaining the temperature at −78 °C, and the reaction was allowed to proceed overnight with stirring after warming to room temperature. The reaction mixture was washed with saturated aqueous NH_4Cl (10 mL), extracted with EtOAc (2 × 20 mL), the organic phase was separated, dried over Na_2SO_4, and the solvent was evaporated in vacuo to give a crude oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (3:1, v/v) as eluent to afford the respective title compound **11f−n** and **15a−c** in 40−62% yield. Some physical and spectroscopic data for **11f−n** and **15a−c** are listed below.

3-(4-Methylsulfanylphenyl)-1-(3-methoxyphenyl)prop-2-yn-1-ol (11f). The product was obtained as a pale yellow oil (1.52 g, 55%): IR (film) 3223 (OH), 2218 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.24 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 5.66 (d, J = 6.1 Hz, 1H, C*H*OH), 6.88 (dd, J = 7.9, 2.4 Hz, 1H, methoxyphenyl H-4), 7.15−7.35 (m, 5H, methylsulfanylphenyl H-3, H-5; methoxyphenyl H-2, H-5, H-6), 7.37 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{17}H_{16}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-propylphenyl)prop-2-yn-1-ol (11g). The product was obtained as a brownish oil (1.15 g, 40%): IR (film) 3256 (OH), 2221 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, J = 7.0 Hz, 3H, $CH_2CH_2CH_3$), 1.59−1.71 (m, 2H, $CH_2CH_2CH_3$), 2.19 (br s, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 2.58 (t, J = 7.0 Hz, 2H, $CH_2CH_2CH_3$), 5.65 (br s, 1H, C*H*OH), 7.16 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.19 (d, J = 8.8 Hz, 2H, propylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.51 (d, J = 8.8 Hz, 2H, propylphenyl H-2, H-6). Anal. ($C_{19}H_{20}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-butylphenyl)prop-2-yn-1-ol (11h). The product was obtained as a brownish oil (1.69 g, 56%): IR (film) 3215 (OH), 2209 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.87 (t, J = 7.0 Hz, 3H, CH_2CH_3), 1.24−1.63 [m, 4H, (CH_2)$_2$], 2.22 (br s, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 2.58 (t, J = 7.0 Hz, 2H, aromatic-C*H*$_2$), 5.66 (br s, 1H, C*H*OH), 7.15 (m, 4H, methylsulfanylphenyl H-3, H-5; butylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.51 (d, J = 7.9 Hz, 2H, butylphenyl H-2, H-6). Anal. ($C_{20}H_{22}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-ol (11i). The product was obtained as a yellow oil (1.85 g, 64%): IR (film) 3217 (OH), 2211 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.27−1.29 [d, J = 6.7 Hz, 6H, CH(C*H*$_3$)$_2$], 2.19 (br s, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 2.89−2.98 [m, 1H, C*H*(CH$_3$)$_2$], 5.65 (br s, 1H, C*H*OH), 7.16−7.32 (m, 4H, methylsulfanylphenyl H-3, H-5; isopropylphenyl H-3, H-5), 7.37 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.53 (d, J = 8.2 Hz, 2H, isopropylphenyl H-2, H-6). Anal. ($C_{19}H_{20}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-cyanophenyl)prop-2-yn-1-ol (11j). The product was obtained as a brown oil (1.22 g, 45%): IR (film) 3382 (OH), 2221 (C≡N), 2206 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.41 (d, J = 5.8 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 5.74 (d, J = 5.8 Hz, 1H, C*H*OH), 7.17 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.35 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.69 (d, J = 8.5 Hz, 2H, cyanophenyl H-2, H-6), 7.73 (d, J = 8.5 Hz, 2H, cyanophenyl H-3, H-5). Anal. ($C_{17}H_{13}NOS$): C, H, N.

3-(4-Methylsulfanylphenyl)-1-(3,4-difluorophenyl)prop-2-yn-1-ol (11k). The product was obtained as a brown oil (1.45 g, 50%): IR (film) 3219 (OH), 2228 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.34 (d, J = 5.8 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 5.64 (d, J = 5.8 Hz, 1H, C*H*OH), 7.14−7.23 (m, 3H, methylsulfanylphenyl H-3, H-5; difluorophenyl H-5), 7.31−7.35 (m, 1H, difluorophenyl H-2), 7.36 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.42 (dddd, J = 8.5, 5.5, 3.0, 1.8 Hz, 1H, difluorophenyl H-6). Anal. ($C_{16}H_{12}F_2OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(3,4-dimethoxyphenyl)prop-2-yn-1-ol (11*l*). The product was obtained as a yellow oil (1.96 g, 64%): IR (film) 3211 (OH), 2213 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.24 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 3.88 (s, 3H, 4-OMe), 3.91 (s, 3H, 3-OMe), 5.63 (d, J = 6.1 Hz, 1H, C*H*OH), 6.85 (d, J = 7.9 Hz, 1H, dimethoxyphenyl H-5), 7.17−7.20 (m, 4H, methylsulfanylphenyl H-3, H-5; dimethoxyphenyl H-2, H-6), 7.36 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{18}H_{18}O_3S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-ol (11m). The product was obtained as a pale yellow oil (1.94 g, 58%): IR (film) 3308 (OH), 2224 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.29 (d, J = 5.8 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 3.90 [s, 9H, (OC*H*$_3$)$_3$], 5.62 (d, J = 5.8 Hz, 1H, C*H*OH), 6.86 (s, 2H, trimethoxyphenyl H-2, H-6), 7.17 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{19}H_{20}O_4S$): C, H.

4-[3-(4-Methylsulfanylphenyl)prop-2-yn-1-ol]benzoic acid methyl ester (11n). The product was obtained as a brown oil (1.21 g, 40%): IR (film) 3221 (OH), 2218 (C≡C), 1640 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43 (br s, 1H, CHO*H*), 2.48 (s, 3H, SC*H*$_3$), 3.98 (s, 3H, COOC*H*$_3$), 5.73 (1H, C*H*OH), 7.16 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.35 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.66 (d, J = 8.5 Hz, 2H, benzoic acid methyl ester H-2, H-6), 8.06 (d, J = 8.5 Hz, 2H, benzoic acid methyl ester H-3, H-5). Anal. ($C_{18}H_{16}O_3S$): C, H.

3-(4-Methylsulfanylphenyl)-1-furan-3-yl-prop-2-yn-1-ol (15a). The product was obtained as a dark brown oil (1.47 g, 62%): IR (film) 3220 (OH), 2218 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17 (d, J = 6.7 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 5.62 (d, J = 6.7 Hz, 1H, C*H*OH), 6.58 (br s, 1H, furanyl H-4), 7.17 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.36 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.43 (br s, 1H, furanyl H-2), 7.60 (br s, 1H, furanyl H-5). Anal. ($C_{14}H_{12}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-naphthalen-1-yl-prop-2-yn-1-ol (15b). The product was obtained as a yellowish brown oil (1.82 g, 61.6%): IR (film) 3218 (OH), 2211 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.38 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 6.35 (d, J = 6.1 Hz, 1H, C*H*OH), 7.16 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.48−7.90 (m, 6H, naphthyl H-2, H-3, H-4, H-5, H-6, H-7), 8.37−8.40 (m, 1H, naphthyl H-8). Anal. ($C_{20}H_{16}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methoxynaphthalen-1-yl)-prop-2-yn-1-ol (15c). The product was obtained as a yellowish brown oil (1.89 g, 58%): IR (film) 3232 (OH), 2211 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.28 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 4.03 (s, 3H, OC*H*$_3$), 6.27 (d, J = 6.1 Hz, 1H, C*H*OH), 6.80 (d, J = 7.9 Hz, 1H, methoxynaphthyl H-3), 7.16 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.38 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.52−7.61 (m, 2H, methoxynaphthyl H-6, H-7), 7.83 (d, J = 7.9 Hz, 1H, methoxynaphthyl H-2), 8.33−8.36 (m, 2H, methoxynaphthyl H-5, H-8). Anal. ($C_{21}H_{18}O_2S$): C, H.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ones (12 and 16a−c). To a stirred solution of the respective 1,3-diarylprop-2-yn-1-ol (**11** and **15a−c**; 4.5 mmol) in acetone (25 mL) was added activated manganese IV oxide (7.8 g, 90 mmol), and the reaction mixture was stirred for 2−3 h at 25 °C after which MnO_2 was filtered off, and the organic solvent was removed in vacuo to give the title compound (**12f−n** and **16a−c**) in good yield (44−65%). Some physical and spectroscopic data for **12f−n** and **16a−c** are listed below.

3-(4-Methylsulfanylphenyl)-1-(3-methoxyphenyl)prop-2-yn-1-one (12f). The product was obtained as a yellow solid by the oxidation of **11f** in the presence of MnO_2 (0.76 g, 60.4%): mp 53−55 °C; IR (film) 2209 (C≡C), 1625 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 7.17 (dd, J = 7.9, 2.4 Hz, 1H, methoxyphenyl H-4), 7.24 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.40 (t, J = 8.5 Hz, 1H, methoxyphenyl H-5), 7.58 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.70 (br s, 1H, methoxyphenyl H-2), 7.83 (br, d, J = 7.6 Hz, methoxyphenyl H-6). Anal. ($C_{17}H_{14}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-propylphenyl)prop-2-yn-1-one (12g). The product was obtained as an oil by the oxidation of **11g** in the presence of MnO_2 (0.71 g, 54%): IR (film) 2205 (C≡C), 1629 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.97 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.65−1.73 (m, 2H, $CH_2CH_2CH_3$), 2.53 (s, 3H, SCH_3), 2.66 (t, J = 7.3 Hz, 2H, C$H_2CH_2CH_3$), 7.23 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.31 (d, J = 8.2 Hz, 2H, propylphenyl H-3, H-5), 7.57 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.12 (d, J = 8.2 Hz, 2H, propylphenyl H-2, H-6). Anal. ($C_{19}H_{18}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-butylphenyl)prop-2-yn-1-one (12h). The product was obtained as an oil by the oxidation of **11h** in the presence of MnO_2 (0.70 g, 51%): IR (film) 2202 (C≡C), 1623 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.26−1.69 [m, 4H, (CH_2)$_2$$CH_3$], 2.53 (s, 3H, SC$H_3$), 2.65 (t, J = 7.3 Hz, 2H, aromatic-CH_2), 7.21 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.30 (d, J = 8.5 Hz, 2H, butylphenyl H-3, H-5), 7.58 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.13 (d, J = 8.5 Hz, 2H, butylphenyl H-2, H-6). Anal. ($C_{20}H_{20}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (12i). The product was obtained as a yellowish oil by the oxidation of **11i** in the presence of MnO_2 (0.75 g, 57%): IR (film) 2208 (C≡C), 1632 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28−1.31 [d, J = 6.7 Hz, 6H, CH(CH_3)$_2$], 2.53 (s, 3H, SCH_3), 2.89−2.98 [m, 1H, CH(CH_3)$_2$], 7.24 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.36 (d, J = 8.8 Hz, 2H, isopropylphenyl H-3, H-5), 7.57 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.13 (d, J = 8.8 Hz, 2H, isopropylphenyl H-2, H-6). Anal. ($C_{19}H_{18}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-cyanophenyl)prop-2-yn-1-one (12j). The product was obtained as a yellow solid by the oxidation of **11j** in the presence of MnO_2 (0.50 g, 40%): mp 149−151 °C; IR (film) 2201 (C≡N), 2193 (C≡C), 1640 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H, SCH_3), 7.26 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.59 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.82 (d, J = 8.2 Hz, 2H, cyanophenyl H-3, H-5), 8.29 (d, J = 8.2 Hz, 2H, cyanophenyl H-2, H-6). Anal. ($C_{17}H_{11}NOS$): C, H, N.

3-(4-Methylsulfanylphenyl)-1-(3,4-difluorophenyl)prop-2-yn-1-one (12k). The product was obtained as an oil by the oxidation of **11k** in the presence of MnO_2 (0.68 g, 52.6%): IR (film) 2186 (C≡C), 1633 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H, SCH_3), 7.25−7.36 (m, 3H, methylsulfanylphenyl H-3, H-5; difluorophenyl H-5), 7.58 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.98−8.05 (m, 2H, difluorophenyl H-2, H-6). Anal. ($C_{16}H_{10}F_2OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(3,4-dimethoxyphenyl)prop-2-yn-1-one (12l). The product was obtained as an oil by the oxidation of **11*l*** in the presence of MnO_2 (0.76 g, 54%): IR (film) 2195 (C≡C), 1638 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 3.95 (s, 3H, 4-OMe), 3.97 (s, 3H, 3-OMe), 6.91 (d, J = 8.5 Hz, 1H, dimethoxyphenyl H-5), 7.23 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.55 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.67 (br s, 1H, dimethoxyphenyl H-2), 7.91 (d, J = 8.5 Hz, 1H, dimethoxyphenyl H-6). Anal. ($C_{18}H_{16}O_3S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (12m). The product was obtained as a white solid by the oxidation of **11m** in the presence of MnO_2 (0.66 g, 43.4%): mp 88−90 °C; IR (film) 2206 (C≡C), 1612 (C═C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.53 (s, 3H, SCH_3), 3.96 [s, 9H, (OCH_3)$_3$], 7.25 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.50 (s, 2H, trimethoxyphenyl H-2, H-6), 7.55 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{19}H_{18}O_4S$): C, H.

4-[3-(4-Methylsulfanylphenyl)prop-2-yn-1-one]benzoic Acid Methyl Ester (12n). The product was obtained as a yellow solid by the oxidation of **11n** in the presence of MnO_2 (0.81 g, 58%): mp 143−145 °C; IR (film) 2208 (C≡C), 1642 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.54 (s, 3H, SCH_3), 3.98 (s, 3H, COOCH_3), 7.25 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.59 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.17 (d, J = 8.2 Hz, 2H, benzoic acid methyl ester H-2, H-6), 8.26 (d, J = 8.2 Hz, 2H, benzoic acid methyl ester H-3, H-5). Anal. ($C_{18}H_{14}O_3S$): C, H.

3-(4-Methylsulfanylphenyl)-1-furan-3-yl-prop-2-yn-1-one (16a). The product was obtained as a brown solid by the oxidation of **15a** in the presence of MnO_2 (0.57 g, 52.6%): mp 83−85 °C; IR (film) 2213 (C≡C), 1625 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 6.88 (br d, J = 1.8 Hz, 1H, furanyl H-4), 7.23 (d, J = 8.5 Hz, 2 H, methylsulfanylphenyl H-3, H-5), 7.47−7.49 (m, 1H, furanyl H-5), 7.52 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.23 (br s, 1H, furanyl H-2). Anal. ($C_{14}H_{10}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-naphthalen-1-yl-prop-2-yn-1-one (16b). The product was obtained as a yellow solid by the oxidation of **15b** in the presence of MnO_2 (0.88 g, 65%): mp 113−115 °C; IR (film) 2206 (C≡C), 1628 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 7.22 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.56−7.72 (m, 5H, methylsulfanylphenyl H-2, H-6; naphthyl H-3, H-6, H-7), 7.91−7.94 (m, 1H, naphthyl H-5), 8.09−8.12 (m, 1H, naphthyl H-4), 8.62−8.65 (m, 1H, naphthyl H-2), 9.21−9.24 (m, 1H, naphthyl H-8). Anal. ($C_{20}H_{14}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methoxynaphthalen-1-yl)-prop-2-yn-1-one (16c). The product was obtained as a yellow solid by the oxidation of **15c** in the presence of MnO_2 (0.88 g, 59%): mp 105−107 °C; IR (film) 2218 (C≡C) 1614 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, SCH_3), 4.12 (s, 3H, OCH_3), 6.91 (d, J = 8.2 Hz, 1H, methoxynaphthyl H-3), 7.24 (d, J = 8.2 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.54−7.73 (m, 4H, methylsulfanylphenyl H-2, H-6; methoxynaphthyl H-6, H-7), 8.34−8.36 (m, 1H, methoxynaphthyl H-5), 8.68 (d, J = 8.2 Hz, 1H, methoxynaphthyl H-2), 9.37−9.39 (m, 1H, methoxynaphthyl H-8). Anal. ($C_{21}H_{16}O_2S$): C, H.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ones (13b−j, 13l, 13n−p and 17a−c). An aqueous solution of Oxone (50% w/v, 3.24 mmol) was added dropwise to a stirred solution of a 1,3-diarylprop-2-yn-1-one (**12** and **16a−c**, 1.08 mmol) possessing a 4-methylsulfanyl substituent on the C-3 phenyl ring in 1,4-dioxane (10 mL) at 0 °C. The reaction was allowed to proceed with stirring at 25 °C for 3−4 h. The reaction mixture was diluted with water (15 mL), extracted with EtOAc (3 × 25 mL), the EtOAc fraction was washed successively with brine solution and water (15 mL each), the organic phase was separated, dried over Na_2SO_4, and the solvent was removed in vacuo to give a crude product. This crude product was purified by silica gel column chromatography using ethyl acetate−hexanes (2:1, v/v or 3:1, v/v) as eluent to afford the respective title compound **13b−j**, **13l**, **13n−p** and **17a−c** in 60−90% yield. Some physical and spectroscopic data for **13b−p** and **17a−c** are listed below.

3-(4-Methanesulfonylphenyl)-1-(4-tolyl)prop-2-yn-1-one (13b). The product was obtained as a white solid by oxidation of **12b** in the presence of aqueous Oxone solution (0.27 g, 85%): mp 116−118 °C; IR (film) 2204 (C≡C), 1620 (C═O), 1317, 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, CH_3), 3.10 (s, 3H, SO_2CH_3), 7.32 (d, J = 7.9 Hz, 2H, tolyl H-3, H-5), 7.85 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.09 (d, J = 7.9 Hz, 2H, tolyl H-2, H-6). Anal. ($C_{17}H_{14}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-propylphenyl)prop-2-yn-1-one (13c). The product was obtained as a yellow oil by oxidation of **12g** in the presence of aqueous Oxone solution (0.27 g, 78%): IR (film) 2232 (C≡C), 1636 (C═O), 1317, 1150 (SO_2) cm^{-1}; ^1H

NMR ($CDCl_3$): δ 0.95 (t, J = 7.3 Hz, 3H, $CH_2CH_2CH_3$), 1.60−1.73 (m, 2H, $CH_2CH_2CH_3$), 2.67 (t, J = 7.3 Hz, 2H, $CH_2CH_2CH_3$), 3.10 (s, 3H, SO_2CH_3), 7.31 (d, J = 8.2 Hz, 2H, propylphenyl H-3, H-5), 7.85 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.11 (d, J = 8.2 Hz, 2H, propylphenyl H-2, H-6). Anal. ($C_{19}H_{18}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-butylphenyl)prop-2-yn-1-one (13d). The product was obtained as a yellow oil by oxidation of **12h** in the presence of aqueous Oxone solution (0.28 g, 76%): IR (film) 2198 (C≡C), 1624 (C═O), 1314, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.98 (t, J = 7.3 Hz, 3H, CH_2CH_3), 1.32−1.39 (m, 2H, CH_2CH_3), 1.57−1.59 (m, 2H, $CH_2CH_2CH_3$), 2.69 (t, J = 7.3 Hz, 2H, aromatic-CH_2), 3.10 (s, 3H, SO_2CH_3), 7.33 (d, J = 8.2 Hz, 2H, butylphenyl H-3, H-5), 7.85 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.11 (d, J = 8.2 Hz, 2H, butylphenyl H-2, H-6). Anal. ($C_{20}H_{20}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-isopropylphenyl)prop-2-yn-1-one (13e). The product was obtained as pale yellow solid by oxidation of **12i** in the presence of aqueous Oxone solution (0.30 g, 85%): mp 182−184 °C; IR (film) 2186 (C≡C), 1630 (C═O), 1310, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.29 [d, J = 6.7 Hz, 6H, $CH(CH_3)_2$], 2.97−3.04 [m, 1H, $CH(CH_3)_2$], 3.10 (s, 3H, SO_2CH_3), 7.38 (d, J = 8.2 Hz, 2H, isopropylphenyl H-3, H-5), 7.85 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.12 (d, J = 8.2 Hz, 2H, isopropylphenyl H-2, H-6). Anal. ($C_{19}H_{18}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-trifluoromethylphenyl)-prop-2-yn-1-one (13f). The product was obtained as a yellow solid by oxidation of **12e** in the presence of aqueous Oxone solution (0.29 g, 78%): yellow solid; mp 151−153 °C; IR (film) 2191 (C≡C), 1632 (C═O), 1322, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.81 (d, J = 8.2 Hz, 2H, trifluoromethylphenyl H-3, H-5), 7.87 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.03 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.31 (d, J = 8.2 Hz, 2H, trifluoromethylphenyl H-2, H-6). Anal. ($C_{17}H_{11}F_3O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-cyanophenyl)prop-2-yn-1-one (13g). The product was obtained as a white solid by oxidation of **12j** in the presence of aqueous Oxone solution (0.28 g, 85%): mp 183−185 °C; IR (film) 2220 (C≡N), 2200 (C≡C), 1640 (C═O), 1311, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.84 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.88 (d, J = 8.5 Hz, 2H, cyanophenyl H-3, H-5), 8.03 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.29 (d, J = 8.5 Hz, 2H, cyanophenyl H-2, H-6). Anal. ($C_{17}H_{11}NO_3S$): C, H, N.

3-(4-Methanesulfonylphenyl)-1-(4-fluorophenyl)prop-2-yn-1-one (13h). The product was obtained by oxidation of **12d** in the presence of aqueous Oxone solution (0.26 g, 81%): yellow solid; mp 142−144 °C; IR (film) 2200 (C≡C), 1647 (C═O), 1309, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 7.19 (dd, J = 8.5, 8.5 Hz, 2H, fluorophenyl H-3, H-5), 7.85 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.01 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.23 (dd, J = 8.5, 5.5 Hz, 2H, fluorophenyl H-2, H-6). Anal. ($C_{16}H_{11}FO_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3,4-difluorophenyl)prop-2-yn-1-one (13i). The product was obtained as a yellow solid by oxidation of **12k** in the presence of aqueous Oxone solution (0.26 g, 76%): mp 149−151 °C; IR (film) 2190 (C≡C), 1633 (C═O), 1318, 1152 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.30−7.39 (m, 1H, difluorophenyl H-5), 7.86 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.98−8.05 (m, 4H, methanesulfonylphenyl H-3, H-5; difluorophenyl H-2, H-6). Anal. ($C_{16}H_{10}F_2O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (13j). The product was obtained as a white solid by oxidation of **12c** in the presence of aqueous Oxone solution (0.29 g, 86%): mp 151−153 °C; IR (film) 2195 (C≡C), 1634 (C═O), 1315, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.92 (s, 3H, OCH_3), 7.00 (d, J = 8.8 Hz, 2H, methoxyphenyl H-3, H-5), 7.84 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.17 (d, J = 8.8 Hz, 2H, methoxyphenyl H-2, H-6). Anal. ($C_{17}H_{14}O_4S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3-methoxyphenyl)prop-2-yn-1-one (13l). The product was obtained as a white solid by oxidation of **12f** in the presence of aqueous Oxone solution (0.26 g, 77%): mp 134−136 °C; IR (film) 2199 (C≡C), 1632 (C═O), 1333, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.90 (s, 3H, OCH_3), 7.20 (dd, J = 8.5, 2.7 Hz, 1H, methoxyphenyl H-4), 7.44 (t, J = 8.5 Hz, 1H, methoxyphenyl H-5), 7.68 (br, s, 1H, methoxyphenyl H-2), 7.83−7.88 (m, 3H, methoxyphenyl H-6, methanesulfonylphenyl H-2, H-6), 8.01 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{17}H_{14}O_4S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3,4-dimethoxyphenyl)prop-2-yn-1-one (13n). The product was obtained as a white solid by oxidation of **12l** in the presence of aqueous Oxone solution (0.31 g, 85%): mp 144−146 °C; IR (film) 2187 (C≡C), 1626 (C═O), 1310, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.95 (s, 3H, 4-OMe), 3.98 (s, 3H, 3-OMe), 6.97 (d, J = 8.5 Hz, 1H, dimethoxyphenyl H-5), 7.66 (br s, 1H, dimethoxyphenyl H-2), 7.83 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.91 (d, J = 8.5 Hz, 1H, dimethoxyphenyl H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{18}H_{16}O_5S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-yn-1-one (13o). The product was obtained as a white solid by oxidation of **12m** in the presence of aqueous Oxone solution (0.31 g, 78%): mp 154−155 °C; IR (film) 2197 (C≡C), 1622 (C═O), 1320, 1158 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.98 [s, 9H, $(OCH_3)_3$], 7.48 (s, 2H, trimethoxyphenyl H-2, H-6), 7.83 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.01 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{19}H_{18}O_6S$): C, H.

4-[3-(4-Methanesulfonylphenyl)prop-2-yn-1-one]benzoic Acid Methyl Ester (13p). The product was obtained as a white solid by oxidation of **12n** in the presence of aqueous Oxone solution (0.31 g, 85%): mp 189−191 °C; IR (film) 2211 (C≡C), 1645 (C═O), 1317, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 3.98 (s, 3H, $COOCH_3$), 7.85 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.02 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.19 (d, J = 8.5 Hz, 2H, benzoic acid methyl ester H-2, H-6), 8.25 (d, J = 8.5 Hz, 2H, benzoic acid methyl ester H-3, H-5). Anal. ($C_{18}H_{14}O_5S$): C, H.

3-(4-Methanesulfonylphenyl)-1-furan-3-yl-prop-2-yn-1-one (17a). The product was obtained as a yellow solid by oxidation of **16a** in the presence of aqueous Oxone solution (0.26 g, 88%): mp 155−157 °C; IR (film) 2218 (C≡C), 1622 (C═O), 1311, 1154 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 6.89 (br d, J = 1.8 Hz, 1H, furanyl H-4), 7.50−7.51 (m, 1H, furanyl H-5), 7.81 (d, J = 8.2 Hz, 2 H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.26 (br s, 1H, furanyl H-2). Anal. ($C_{14}H_{10}O_4S$): C, H.

3-(4-Methanesulfonylphenyl)-1-naphthalen-1-yl-prop-2-yn-1-one (17b). The product was obtained as a white solid by oxidation of **16b** in the presence of aqueous Oxone solution (0.29 g, 81%): mp 132−134 °C; IR (film) 2218 (C≡C), 1613 (C═O), 1317, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.61−7.75 (m, 3H, naphthyl H-3, H-6, H-7), 7.86 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.89−7.93 (m, 1H, naphthyl H-5), 8.01 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.13−8.16 (m, 1H, naphthyl H-4), 8.62−8.65 (m, 1H, naphthyl H-2), 9.23−9.26 (m, 1H, naphthyl H-8). Anal. ($C_{20}H_{14}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-methoxynaphthalen-1-yl)-prop-2-yn-1-one (17c). The product was obtained as a white solid by oxidation of **16c** in the presence of aqueous Oxone solution (0.32 g, 82%): mp 175−177 °C; IR (film) 2218 (C≡C), 1622 (C═O), 1311, 1150 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 4.13 (s, 3H, OCH_3), 6.92 (d, J = 8.2 Hz, 1H, methoxynaphthyl H-3), 7.56−7.76 (m, 2H, methoxynaphthyl H-6, H-7),

7.85 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.00 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.35−8.38 (m, 1H, methoxynaphthyl H-5), 8.66 (d, J = 8.2 Hz, 1H, methoxynaphthyl H-2), 9.36−9.39 (m, 1H, naphthyl H-8). Anal. ($C_{21}H_{16}O_4S$): C, H.

General Procedure for the Synthesis of 3-(4-Methanesulfonylphenyl)-1-(4-hydroxyphenyl)prop-2-yn-1-one (13k) and 3-(4-Methanesulfonylphenyl)-1-(3-hydroxyphenyl)prop-2-yn-1-one (13m). To a stirred solution of **13j** or **13l** (1.1 mmol) in freshly dried CH_2Cl_2 under an argon atmosphere at 0 °C, boron tribromide (0.40 mL, 4.3 mmol) was added dropwise and the reaction was stirred at −5 to 0 °C for 1 h, after which the reaction mixture was quenched with crushed ice, extracted with EtOAc (3 × 20 mL), dried over Na_2SO_4 and the solvent was removed in vacuo to afford a dark brown oil. This oil was purified by silica gel column chromatography using CH_2Cl_2–ethyl acetate (5:1, v/v or 4:1, v/v) as eluent, using two consecutive column separations, to afford the respective title compound **13k** and **13m** in 50−55% yield. Some physical and spectroscopic data for **13k** and **13m** are listed below.

3-(4-Methanesulfonylphenyl)-1-(4-hydroxyphenyl)prop-2-yn-1-one (13k). The product was obtained as a yellow solid from **13j** (0.18 g, 56%): mp 211−213 °C; IR (film) 3205 (OH), 2204 (C≡C), 1642 (C═O), 1323, 1170 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.05 (s, 3H, SO_2CH_3), 6.77 (d, J = 8.5 Hz, 2H, hydroxyphenyl H-3, H-5), 7.29 (s, 1H, OH), 7.68 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.83 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 7.89 (d, J = 8.5 Hz, 2H, hydroxyphenyl H-2, H-6). Anal. ($C_{16}H_{12}O_4S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3-hydroxyphenyl)prop-2-yn-1-one (13m). The product was obtained as a yellow solid from **13l** (0.17 g, 52%): mp 178−180 °C; IR (film) 3207 (OH), 2185 (C≡C), 1635 (C═O), 1313, 1156 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.06 (s, 3H, SO_2CH_3), 7.00 (dd, J = 7.9, 2.4 Hz, 1H, hydroxyphenyl H-4), 7.21 (t, J = 7.9 Hz, 1H, hydroxyphenyl H-5), 7.34−7.37 (m, 2H, hydroxyphenyl H-2, H-6), 7.56 (s, 1H, OH), 7.83 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.91 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{16}H_{12}O_4S$): C, H.

General Procedure for the Synthesis of 4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (19a) and 3-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzaldehyde (19b). To a stirred solution of the aldehyde (**18a** or **18b**; 6.1 mmol) in freshly dried THF (15 mL) kept under an argon atmosphere at 25 °C, NaH (0.29 g, 12.0 mmol) was slowly added, immediately after which *tert*-butyldimethylsilyl chloride (TBDMSCl, 1.1 g, 6.7 mmol) was added and the reaction mixture was stirred at 25 °C for 2−3 h. The reaction mixture was washed with 1N HCl (10 mL), extracted with EtOAc (3 × 20 mL), the organic phase was separated, dried over Na_2SO_4, and the organic solvent was removed in vacuo to afford the respective title compounds **19a** and **19b** in 65−70% yield. Some physical and spectroscopic data for **19a** and **19b** are listed below.

4-(*tert*-Butyldimethylsilyloxy)-3-methoxybenzaldehyde (19a). The product was obtained as an oil from **18a** (1.90 g, 65%): IR (film) 1689 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.18 [s, 6H, Si(CH_3)$_2$], 1.00 [s, 9H, C(CH_3)$_3$], 3.90 (s, 3H, OCH_3), 6.95 (d, J = 8.5 Hz, 1H, benzaldehyde H-5), 7.37 (d, J = 2.1 Hz, 1H, benzaldehyde H-2), 7.46−7.50 (m, 1H, benzaldehyde H-6), 9.83 (s, 1H, CHO).

3-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzaldehyde (19b). The product was obtained as a yellow solid from **18b** (2.05 g, 70%): IR (film) 1693 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.18 [s, 6H, Si(CH_3)$_2$], 1.00 [s, 9H, C(CH_3)$_3$], 3.89 (s, 3H, OCH_3), 6.94 (d, J = 8.5 Hz, 1H, benzaldehyde H-5), 7.37 (d, J = 1.8 Hz, 1H, benzaldehyde H-2), 7.46−7.49 (m, 1H, benzaldehyde H-6), 9.82 (s, 1H, CHO).

General Procedure for the Synthesis of 3-(4-Methylsulfanylphenyl)-1-[4-(*tert*-butyldimethylsilyloxy)-3-methoxyphenyl]-prop-2-yn-1-ol (20a) and 3-(4-Methylsulfanylphenyl)-1-[3-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl]prop-2-yn-1-ol (20b). Compounds **20a**,**b** for which the physical and spectroscopic data are listed below, were prepared using a procedure similar to that described previously for the synthesis of compounds **11** and **15a**−**c**.

3-(4-Methylsulfanylphenyl)-1-[4-(*tert*-butyldimethylsilyloxy)-3-methoxyphenyl]prop-2-yn-1-ol (20a). The product was obtained as an oil by the reaction of **9** with **19a** (1.53 g, 38%): IR (film) 3220 (OH), 2218 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.16 [s, 6H, Si(CH_3)$_2$], 1.00 [s, 9H, C(CH_3)$_3$], 2.20 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 5.62 (d, J = 6.1 Hz, 1H, C*H*OH), 6.85 (d, J = 8.2 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-5), 7.00−7.13 (m, 2H, *tert*-butyldimethylsilyloxyphenyl H-2, H-6), 7.17 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{23}H_{30}O_3SSi$): C, H.

3-(4-Methylsulfanylphenyl)-1-[3-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl]prop-2-yn-1-ol (20b). The product was obtained as an oil by the reaction of **9** with **19b** (1.25 g, 31%): IR (film) 3210 (OH), 2208 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.16 [s, 6H, Si(CH_3)$_2$], 1.01 [s, 9H, C(CH_3)$_3$], 2.15 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 3.82 (s, 3H, OCH_3), 5.57 (d, J = 6.1 Hz, 1H, C*H*OH), 6.85 (d, J = 8.2 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-5), 7.11−7.24 (m, 4H, methylsulfanylphenyl H-3, H-5; *tert*-butyldimethylsilyloxyphenyl H-2, H-6), 7.36 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6). Anal. ($C_{23}H_{30}O_3SSi$): C, H.

General Procedure for the Synthesis of 3-(4-Methylsulfanylphenyl)-1-[4-(*tert*-butyldimethylsilyloxy)-3-methoxyphenyl]-prop-2-yn-1-one (21a) and 3-(4-Methylsulfanylphenyl)-1-[3-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl]prop-2-yn-1-one (21b). Compounds **21a**,**b** for which the physical and spectroscopic data are listed below, were prepared using a procedure similar to that described previously for the synthesis of compounds **12** and **16a**−**c**.

3-(4-Methylsulfanylphenyl)-1-[4-(*tert*-butyldimethylsilyloxy)-3-methoxyphenyl]prop-2-yn-1-one (21a). The product was obtained as an oil by the oxidation of **20a** in the presence of MnO_2 (0.83 g, 45%): IR (film) 2215 (C≡C), 1660 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.20 [s, 6H, Si(CH_3)$_2$], 1.00 [s, 9H, C(CH_3)$_3$], 2.52 (s, 3H, SCH_3), 3.89 (s, 3H, OCH_3), 6.93 (d, J = 8.2 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-5), 7.22 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.55 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.66 (d, J = 1.8 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-2), 7.81−7.85 (m, 1H, *tert*-butyldimethylsilyloxyphenyl H-6). Anal. ($C_{23}H_{28}O_3SSi$): C, H.

3-(4-Methylsulfanylphenyl)-1-[3-(*tert*-butyldimethylsilyloxy)-4-methoxyphenyl]prop-2-yn-1-one (21b). The product was obtained as an oil by the oxidation of **20b** in the presence of MnO_2 (1.0 g, 54%): IR (film) 2214 (C≡C), 1666 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 0.19 [s, 6H, Si(CH_3)$_2$], 1.01 [s, 9H, C(CH_3)$_3$], 2.51 (s, 3H, SCH_3), 3.90 (s, 3H, OCH_3), 6.94 (d, J = 7.9 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-5), 7.22 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.54 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.68 (d, J = 2.1 Hz, 1H, *tert*-butyldimethylsilyloxyphenyl H-2), 7.86−7.89 (m, 1H, *tert*-butyldimethylsilyloxyphenyl H-6). Anal. ($C_{23}H_{28}O_3SSi$): C, H.

General Procedure for the Synthesis of 3-(4-Methylsulfanylphenyl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-yn-1-one (22a) and 3-(4-Methylsulfanylphenyl)-1-(3-hydroxy-4-methoxyphenyl)prop-2-yn-1-one (22b). To a solution of KOH (0.045 g, 0.80 mmol) in ethanol (4 mL), the TBDMS protected 1,3-diphenylprop-2-yn-1-one (**21a** or **21b,** 0.53 mmol) was added and the reaction was allowed to proceed with stirring at 25 °C for 45 min. Addition of water (10 mL), extraction with EtOAc (3 × 20 mL), drying the extract (Na_2SO_4), and removal of the solvent in vacuo gave an oil. This oil was purified by silica gel column chromatography using ethyl acetate−hexanes (1:3, v/v) as eluent to afford the respective product **22a** and **22b**. Some physical and spectroscopic data for **22a** and **22b** are listed below.

3-(4-Methylsulfanylphenyl)-1-(4-hydroxy-3-methoxyphenyl)-prop-2-yn-1-one (22a). The product was obtained as a yellow solid from **21a** (0.08 g, 52%): mp 109−111 °C; IR (film) 3102 (OH), 2215 (C≡C), 1661 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (s,

3H, SCH_3), 3.99 (s, 3H, OCH_3), 6.16 (br s, 1H, O*H*), 7.01 (d, J = 8.2 Hz, 1H, hydroxyphenyl H-5), 7.23 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.55 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.67 (d, J = 1.8 Hz, 1H, hydroxyphenyl H-2), 7.88−7.92 (m, 1H, hydroxyphenyl H-6). Anal. ($C_{17}H_{14}O_3S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(3-hydroxy-4-methoxyphenyl)-prop-2-yn-1-one (22b). The product was obtained as an oil from **21b** (0.07 g, 48%): IR (film) 3102 (OH), 2207 (C≡C), 1602 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.51 (s, 3H, SCH_3), 4.00 (s, 3H, OCH_3), 5.70 (br s, 1H, O*H*), 6.96 (d, J = 8.2 Hz, 1H, hydroxyphenyl H-5), 7.23 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.57 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.76 (d, J = 1.8 Hz, 1H, hydroxyphenyl H-2), 7.81−7.85 (m, 1H, hydroxyphenyl H-6). Anal. ($C_{17}H_{14}O_3S$): C, H.

General Procedure for the Synthesis of 3-(4-Methanesulfonylphenyl)-1-(4-hydroxy-3-methoxyphenyl)prop-2-yn-1-one (23a) and 3-(4-Methanesulfonylphenyl)-1-(3-hydroxy-4-methoxyphenyl)prop-2-yn-1-one (23b). Compounds **23a**,**b** for which the physical and spectroscopic data are listed below, were prepared using a procedure similar to that described previously for the synthesis of compounds **13b**−**j**, **13l**, **13n**−**p** and **17a**−**c**.

3-(4-Methanesulfonylphenyl)-1-(4-hydroxy-3-methoxyphenyl-)prop-2-yn-1-one (23a). The product was obtained as a white solid by oxidation of **22a** in the presence of aqueous Oxone solution (0.28 g, 81%): mp 194−196 °C; IR (film) 3102 (OH), 2215 (C≡C), 1660 (C═O), 1317, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.10 (s, 3H, SO_2CH_3), 3.97 (s, 3H, OCH_3), 7.00 (d, J = 8.2 Hz, 1H, hydroxyphenyl H-5), 7.63 (d, J = 1.8 Hz, 1H, hydroxyphenyl H-2), 7.81−7.86 (m, 3H, methanesulfonylphenyl H-2, H-6; hydroxyphenyl H-6), 7.99 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.78 (br s, 1H, O*H*). Anal. ($C_{17}H_{14}O_5S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(3-hydroxy-4-methoxyphenyl-)prop-2-yn-1-one (23b). The product was obtained as a white solid by oxidation of **22b** in the presence of aqueous Oxone solution (0.29 g, 85%): mp 195−197 °C; IR (film) 3105 (OH), 2217 (C≡C), 1660 (C═O), 1315, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 3.11 (s, 3H, SO_2CH_3), 3.98 (s, 3H, OCH_3), 6.90 (d, J = 8.2 Hz, 1H, hydroxyphenyl H-5), 7.56 (d, J = 2.1 Hz, 1H, hydroxyphenyl H-2), 7.64−7.67 (m, 1H, hydroxyphenyl H-6), 7.72 (br s, 1H, O*H*), 7.81 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-2, H-6), 7.94 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{17}H_{14}O_5S$): C, H.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ones (25a−c). To a solution of freshly dried THF (10−15 mL) under an argon atmosphere, an acid chloride (**24a**−**c**, 4.0 mmol) and 1-ethynyl-4-methylsulfanylbenzene (**9**, 2.7 mmol) were added. $PdCl_2(PPh_3)_2$ (18 mg, 25.6 μmol) and CuI (16 mg, 84 μmol) were added with stirring for 1−2 min. This was immediately followed by the addition of anhydrous Et_3N (0.5 mL, 3.56 mmol), the reaction was allowed to proceed with stirring for 2−3 h at 25 °C, filtered, washed with ethyl acetate (20 mL), and the solvent from the organic layer was removed in vacuo. The residue obtained was purified by silica gel column chromatography using CH_2Cl_2–ethyl acetate (5:1, v/v or 4:1, v/v) as eluent by two consecutive column purifications, to afford the respective title compound **25a**−**c** in 18−25% yield. Some physical and spectroscopic data for **25a**−**c** are listed below.

3-(4-Methylsulfanylphenyl)-1-isoxazol-5-yl-prop-2-yn-1-one (25a). The product was obtained as a yellow solid by the coupling of **9** with **24a** (0.11 g, 18%): mp 114−116 °C; IR (film) 2205 (C≡C), 1610 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, SCH_3), 7.08 (d, J = 1.8 Hz, 1H, isoxazolyl H-3 or H-4), 7.21 (d, J = 8.8 Hz, 2 H, methylsulfanylphenyl H-3, H-5), 7.59 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.23 (d, J = 1.8 Hz, 1H, isoxazolyl H-4 or H-3). Anal. ($C_{13}H_9NO_2S$): C, H, N.

3-(4-Methylsulfanylphenyl)-1-(4-nitrophenyl)prop-2-yn-1-one (25b). The product was obtained as a yellow solid by the coupling of **9** with **24b** (0.16 g, 21%): mp 165−167 °C; IR (film) 2193 (C≡C), 1640 (C═O), 1530, 1341 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, SCH_3), 7.25 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.59 (d, J = 8.5 Hz, 2H, methylsulfanylphenyl H-2, H-6), 8.35−8.40 (m, 4H, nitrophenyl H-2, H-3, H-5, H-6). Anal. ($C_{16}H_{11}NO_3S$): C, H, N.

3-(4-Methylsulfanylphenyl)-1-(3-nitrophenyl)prop-2-yn-1-one (25c). The product was obtained as a yellow solid by the coupling of **9** with **24c** (0.20 g, 25%): mp 154−156 °C; IR (film) 2191 (C≡C), 1644 (C═O), 1535, 1348 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 7.24 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-3, H-5), 7.63 (d, J = 8.8 Hz, 2H, methylsulfanylphenyl H-2, H-6), 7.72 (t, J = 8.2 Hz, 1H, nitrophenyl H-5), 8.47−8.54 (m, 2H, nitrophenyl H-4, H-6), 9.05 (d, J = 1.8 Hz, 1H, nitrophenyl H-2). Anal. ($C_{16}H_{11}NO_3S$): C, H, N.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ones (26a−c). An aqueous solution of Oxone (50% w/v, 1.62 mmol) was added dropwise to a stirred solution of a 1,3-diarylprop-2-yn-1-one (**25a**−**c**, 0.54 mmol) possessing a *p*-methylsulfanyl substituent on the C-3 phenyl ring in 1,4-dioxane (10 mL) at 0 °C. The reaction was allowed to proceed with stirring at 25 °C for 4−5 h. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (2 × 20 mL), the EtOAc fraction was washed successively with brine solution and water (10 mL each), the organic phase was separated, dried over Na_2SO_4, and the solvent was removed in vacuo to give a crude oil. This oil was purified by silica gel column chromatography using ethyl acetate−hexanes (2:1, v/v or 3:1, v/v) as eluent to afford the respective title compound **26a**−**c** in 80−84% yield. Some physical and spectroscopic data for **26a**−**c** are listed below.

3-(4-Methanesulfonylphenyl)-1-isoxazol-5-yl-prop-2-yn-1-one (26a). The product was obtained as a yellow solid by oxidation of **25a** in the presence of aqueous Oxone solution (0.11 g, 80%): mp 163−165 °C; IR (film) 2212 (C≡C), 1622 (C═O), 1317, 1154 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 7.12 (d, J = 1.8 Hz, 1H, isoxazolyl H-3 or H-4), 7.89 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.03 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.46 (d, J = 1.8 Hz, 1H, isoxazolyl H-4 or H-3). Anal. ($C_{13}H_{11}NO_4S$): C, H, N.

3-(4-Methanesulfonylphenyl)-1-(4-nitrophenyl)prop-2-yn-1-one (26b). The product was obtained as a yellow solid by oxidation of **25b** in the presence of aqueous Oxone solution (0.14 g, 80%): mp 211−213 °C; IR (film) 2193 (C≡C), 1640 (C═O), 1535, 1348 (NO_2), 1317, 1150 (SO_2), cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.88 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.04 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.36−8.42 (m, 4H, nitrophenyl H-2, H-3, H-5, H-6). Anal. ($C_{16}H_{11}NO_5S$): C, H, N.

3-(4-Methanesulfonylphenyl)-1-(3-nitrophenyl)prop-2-yn-1-one (26c). The product was obtained as a yellow solid by oxidation of **25c** in the presence of aqueous Oxone solution (0.15 g, 84%): mp 195−197 °C; IR (film) 2188 (C≡C), 1643 (C═O), 1531, 1341 (NO_2), 1311, 1150 (SO_2), cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.11 (s, 3H, SO_2CH_3), 7.74 (t, J = 8.8 Hz, 1H, nitrophenyl H-5), 7.87 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.05 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5), 8.51−8.55 (m, 2H, nitrophenyl H-4, H-6), 9.04 (d, J = 1.8 Hz, 1H, nitrophenyl H-2). Anal. ($C_{16}H_{11}NO_5S$): C, H, N.

Procedure for the Synthesis of 1,3-Bis-(4-methanesulfonylphenyl)prop-2-yn-1-one (28). An aqueous solution of Oxone (50% w/v, 1.62 mmol) was added dropwise to a stirred solution of 3-(4-methanesulfonylphenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-one (**27**, 0.54 mmol) in 1,4-dioxane (10 mL) at 0 °C. The reaction was allowed to proceed with stirring at 25 °C for 3−4 h. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (2 × 20 mL), the EtOAc fraction was washed successively with brine solution and water (10 mL each), the organic phase was separated, dried over Na_2SO_4, and the solvent was removed in vacuo to give a crude solid which was purified by silica gel column chromatography using ethyl acetate−hexanes (3:1, v/v) as eluent to afford **28** as a white solid (0.14 g, 75%): mp 235−237 °C; IR (film) 2218 (C≡C), 1622 (C═O), 1317, 1150 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.11 (s, 3H, SO_2CH_3), 3.12 (s, 3H, SO_2CH_3), 7.88 (d, J = 8.5 Hz, 2H, ethynylmethanesulfonylbenzene H-2, H-6), 8.04 (d, J = 8.5 Hz, 2H, ethynylmethanesulfonylbenzene H-3, H-5), 8.12

(d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-2, H-6), 8.38 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{17}H_{14}O_5S_2$): C, H.

Cyclooxygenase Inhibition Studies. The ability of the test compounds **13**, **17**, **26**, **27** and **28** 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 the manufacturer's instructions. Cyclooxygenase catalyzes the first step in the biosynthesis of arachidonic acid (AA) to PGH_2. $PGF_2\alpha$, produced from PGH_2 by reduction with stannous chloride, is measured by enzyme immunoassay (ACE competitive EIA). Stock solutions of test compounds were dissolved in a minimum volume of DMSO. Briefly, to a series of supplied reaction buffer solutions (960 μl, 0.1 M Tris-HCl pH 8.0 containing 5 mM EDTA and 2 mM phenol) with either COX-1 or COX-2 (10 μl) enzyme in the presence of heme (10 μl) were added 10 μl of various concentrations of test drug solutions (0.001, 0.01, 0.1, 1, 10 and 100 μM in a final volume of 1 mL). These solutions were incubated for a period of 5 min at 37 °C after which 10 μl of AA (100 μM) solution were added and the COX reaction was stopped by the addition of 50 μl of 1 M HCl after 2 min. $PGF_2\alpha$, produced from PGH_2 by reduction with stannous chloride was measured by enzyme immunoassay. This assay is based on the competition between PGs and a PG-acetylcholinesterase conjugate (PG tracer) for a limited amount of PG antiserum. The amount of PG tracer that is able to bind to the PG antiserum is inversely proportional to the concentration of PGs in the wells since the concentration of PG tracer is held constant while the concentration of PGs varies. This antibody−PG complex binds to a mouse anti-rabbit monoclonal antibody that had been previously attached to the well. The plate is washed to remove any unbound reagents and then Ellman's reagent, which contains the substrate to acetylcholine esterase, is added to the well. The product of this enzymatic reaction produces a distinct yellow color that absorbs at 405 nm. The intensity of this color, determined spectrophotometrically, is proportional to the amount of PG tracer bound to the well, which is inversely proportional to the amount of PGs present in the well during the incubation: Absorbance α [Bound PG Tracer] α 1/PGs. Percent inhibition was calculated by the comparison of compound-treated to various control incubations. The concentration of the test compound causing 50% inhibition ($IC_{50,}$ μM) was calculated from the concentration-inhibition response curve (duplicate determinations).

Lipoxygenase Inhibition Studies. The ability of the test compounds **13**, **17**, **26**, **27** and **28** to inhibit potato 5-LOX (catalog number 60401, Cayman Chemical, Ann Arbor, MI) and soybean 15-LOX (IC_{50} values, μM) was determined using an enzyme immuno assay (EIA) kit (catalog number 760700, Cayman Chemical, Ann Arbor, MI) according to the manufacturer's instructions. The Cayman Chemical lipoxygenase inhibitor screening assay detects and measures the hydroperoxides produced in the lipoxygenation reaction using a purified lipoxygenase. Stock solutions of test compounds were dissolved in a minimum volume of DMSO and were diluted using the supplied buffer solution (0.1 M, Tris-HCl pH 7.4). To a 90 μL solution of 5- or 15-LOX enzyme in 0.1 M, Tris-HCl pH 7.4 buffer, 10 μL of various concentrations of test drug solutions (0.001, 0.01, 0.1, 1and 10 μM in a final volume of 210 μL) were added and the lipoxygenase reaction was initiated by the addition of 10 μL (100 μM) of linoleic acid (LA). After maintaining the 96-well plate on a shaker for 5 min, 100 μL of chromogen was added and the plate was retained on a shaker for 5 min. The lipoxygenase activity was determined after measuring absorbance at a wavelength of 490 nm. Percent inhibition was calculated by the comparison of compound-treated to various control incubations. The concentration of the test compound causing 50% inhibition ($IC_{50,}$ μM) was calculated from the concentration-inhibition response curve (duplicate determinations).

Antiinflammatory Assay. The test compounds were evaluated using the in vivo rat carrageenan-induced foot paw edema model reported previously.[27,28]

Analgesic Assay. Analgesic activity was determined using the 4% sodium chloride-induced writhing (abdominal constriction) assay as described previously.[29]

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 structure of the enzyme COX-1/2 and 15-LOX were 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. In the case of COX-1 (PDB file 1prh) the ligand was suitably positioned in the active site while carefully monitoring nonbonded interactions of the ligand−enzyme assembly and any side chain bumps. The coordinates for 15-LOX was obtained from PDB file1lox and the energy minimized ligand was superimposed on the inhibitor RS75091 after which RS75091 was deleted. In all these experiments 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 ligand−enzyme assembly was then 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 optimal binding orientation of the ligand−enzyme assembly obtained after docking was further minimized for 1000 iterations using the conjugate gradient method until a convergence of 0.001 kcal/mol Å was reached after which $E_{\text{intermolecular}}$ (kcal/mol) of the ligand−enzyme assembly was evaluated.

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Supporting Information Available: A table of microanalytical data is presented for compounds **11**−**13**, **15**−**17**, **20**−**23**, **25**, **26** and **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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