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# Synthesis and biological evaluation of 1,3-diphenylprop-2-yn-1-ones as dual inhibitors of cyclooxygenases and lipoxygenases

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**Abstract**—A new class of 1,3-diphenylprop-2-yn-1-ones possessing a *p*-$MeSO_2$ COX-2 phamacophore on the C-3 phenyl ring was designed for evaluation as dual inhibitors of cyclooxygenase (COX) and lipoxygenase (LOX). Among the group of compounds evaluated, 1-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)prop-2-yn-1-one (**11j**) exhibited excellent COX-2 inhibitory potency (COX-2 $IC_{50}$ = 0.1 μM) and selectivity (SI = 300), whereas 1-(4-cyanophenyl)-3-(4-methanesulfonylphenyl)prop-2-yn-1-one (**11d**) exhibited an optimal combination of COX and LOX inhibition (COX-2 $IC_{50}$ = 1.0 μM; COX-2 SI = 31.5; 5-LOX $IC_{50}$ = 1.0 μM; 15-LOX $IC_{50}$ = 3.2 μM).
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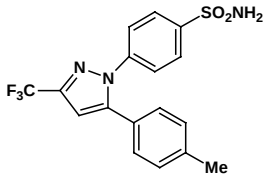
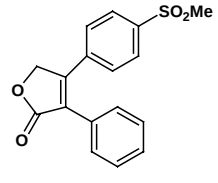
The introduction of selective cyclooxygenase-2 (COX-2) inhibitors, such as celecoxib (**1**) and rofecoxib (**2**), in the late 1990s provided novel anti-inflammatory-analgesic agents with reduced gastrointestinal side effects.[1,2] However, the recent market withdrawal of rofecoxib and valdecoxib due to their adverse cardiovascular side effects clearly delineates the need to develop alternative anti-inflammatory agents with reduced toxicity.[3]

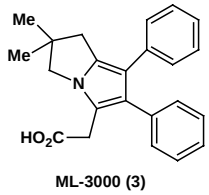
Lipoxygenases (LOXs), which are widely distributed in both the plant and animal kingdoms, belong to a class of non-heme iron-containing enzymes which catalyze dioxygen incorporation into polyunsaturated fatty acids, such as linoleic and arachidonic acid, to form hydroperoxide products.[4] Currently, LOXs are potential targets in the treatment of diseases such as asthma, atherosclerosis, cancer, and a variety of inflammatory conditions. For example, leukotrienes formed via the 5-lipoxygenase (5-LOX) pathway are known to contribute to the pathophysiology of osteoarthritis, asthma, and prostate cancer. Metabolites formed via the 15-lipoxygenase (15-LOX) pathway have been implicated in the oxidative modification of low-density lipoprotein (LDL), ultimately leading to atherosclerosis.[5,6] The dual COX/5-LOX inhibitor ML-3000 (licofelone, **3**) is a potent anti-inflammatory agent with excellent gastrointestinal tolerance, demonstrating platelet function inhibition and an anti-thrombotic effect.[7] Nordihydroguaiaretic acid (NDGA, **4**), a natural dicatechol exhibiting in vivo anti-inflammatory activity, is known to inhibit the LOX isozymes (5-LOX, 12-LOX, and 15-LOX).[8] As part of our ongoing program to design novel anti-inflammatory agents devoid of adverse side effects, we describe herein the synthesis and biological evaluation of a novel class of 1,3-diphenylprop-2-yn-1-ones possessing a *p*-$MeSO_2$ COX-2 pharmacophore on the C-3 phenyl ring as dual inhibitors of COXs and LOXs.



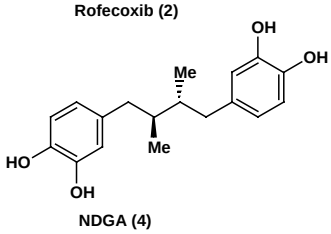
Celecoxib (1)



Rofecoxib (2)



ML-3000 (3)



NDGA (4)

The synthetic strategies used to prepare the target substituted-1,3-diphenylprop-2-yn-1-ones (**11a**–**11k**, **16a** and **16b**) are shown in Schemes 1 and 2. The precursor,

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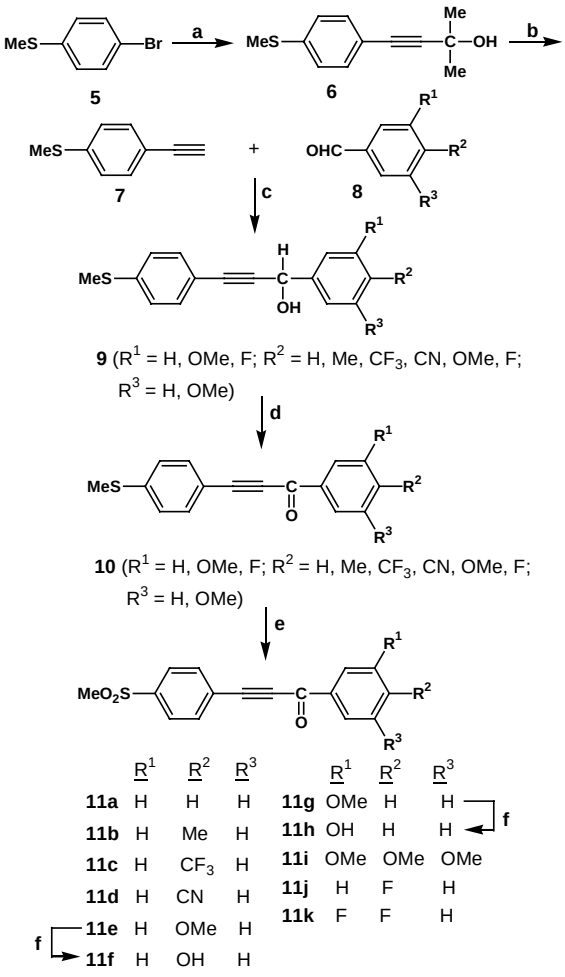
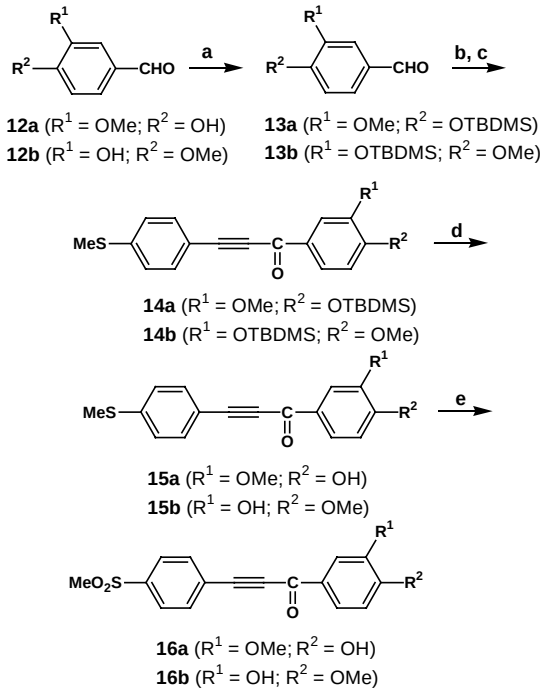



**Scheme 1.** Reagents and conditions: (a) triethylamine, 2-methyl-3-butyn-1-ol, $[(C_6H_5)_3P]_2PdCl_2$, CuI, 70–75 °C, 5–6 h; (b) benzene, NaH, 100–110 °C, 1–1.5 h; (c) THF, −78 °C, *n*-BuLi, and then at −78 °C to 25 °C over night; (d) acetone, $MnO_2$, 25 °C, 2–3 h; (e) 1,4-dioxane, aqueous Oxone®, 25 °C, 3–4 h; (f) $BBr_3$, $CH_2Cl_2$, −5 to 0 °C, 1 h.

1-ethynyl-4-methylsulfanylbenzene (**7**), was prepared in two steps by Sonogashira coupling of 4-bromothioanisole (**5**) with 2-methyl-3-butyn-1-ol in the presence of triethylamine, CuI, and $[(C_6H_5)_3P]_2PdCl_2$ [dichlorobis(triphenylphosphine)palladium], which gave the protected *para*-methylsulfanylphenylacetylene (**6**) in good yield (70–75%). Subsequent removal of the isopropanol moiety using NaH afforded **7** in good yield (40–55%, Scheme 1).[9] The condensation of 1-ethynyl-4-methylsulfanylbenzene (**7**) with a substituted benzaldehyde (**8**) in the presence of *n*-BuLi afforded the 1,3-diphenylprop-2-yn-l-ols **9** (40–58%). Subsequent oxidation of the alcohols **9** using activated $MnO_2$ afforded the corresponding 1,3-diphenylprop-2-yn-l-ones **10** (44–56%) having a C-3 4-methylthiophenyl substituent. Oxone® oxidation of **10** afforded the target 1,3-diphenylprop-2-yn-1-ones **11a**–**11e**,**11g**, and **11i**–**11k** (72–85%) possessing a C-3 4-$MeSO_2$-$C_6H_4$-substituent, as shown in Scheme 1.[10] *O*-Demethylation of **11e** and **11g** using boron tribromide afforded the respective phenol derivatives **11f** and **11h** (50–55%), as shown in Scheme 1.




**Scheme 2.** Reagents and conditions: (a) THF, NaH, TBDMSCl, 25 °C, 2–3 h; (b) 4-MeS-$C_6H_4$C≡CH, THF, −78 °C, *n*-BuLi, −78 °C to 25 °C over night; (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.

Compounds **16a** and **16b** were prepared according to Scheme 2. The *tert*-butyldimethylsilyloxy benzaldehyde regioisomers (**13**) were prepared by the reaction of the respective benzaldehyde (**12**) with *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of NaH[10] (65–70%). Subsequent condensation of **13** with **7** 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 **14** (45–54%). Deprotection of aryl *tert*-butyldimethylsilyl (TBS) ethers (**14**) using KOH in EtOH afforded the respective phenol (**15**, 45–52%)[10], which was then oxidized using aqueous Oxone® to afford **16a** and **16b** (80–85%), as shown in Scheme 2. The 1,3-diphenylprop-2-yn-1-ones (**10**, **11**, and **14**–**16**) are expected to be useful Michael acceptors useful for the synthesis of heterocyles.[10b]

In vitro structure–activity relationships acquired for these 1,3-diphenylprop-2-yn-1-ones (**11**, **16**) 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 $IC_{50} = 1$ to >100 μM range; 5-LOX $IC_{50} = 0.3$ to >10 μM range; 15-LOX $IC_{50} = 0.1$ to >10 μM range; Table 1).

Compound **11a**, having an unsubstituted C-1 phenyl ring, exhibited moderate inhibition of COX-2 (COX-2 $IC_{50} = 10$ μM), but it did not inhibit either 5- or 15-LOX at a concentration of 10 μM. In contrast **11c**, possessing a C-1 *p*-$CF_3$-phenyl substituent, exhibited COX-1 selectivity (COX-1 $IC_{50} = 3.1$ μM; COX-2 $IC_{50} > 100$ μM). Interestingly, introduction of a C-1 *p*-CN-phenyl substituent (**11d**) provided a dual COX

**Table 1.** In vitro COX-1/COX-2 and 5-LOX/15-LOX isozyme assay data for 1,3-diphenylprop-2-yn-1-ones **11a**–**11k**, **16a**, and **16b**

| Compound | $R^1$ | $R^2$ | $R^3$ | COX-1 $IC_{50}$[a] (μM) | COX-2 $IC_{50}$[a] (μM) | COX-2 SI[b] | 5-LOX $IC_{50}$[a] (μM) | 15-LOX $IC_{50}$[a] (μM) |
|---|---|---|---|---|---|---|---|---|
| **11a** | H | H | H | 1.0 | 10.0 | — | >10 | >10 |
| **11b** | H | Me | H | >100 | 33.0 | >3.0 | >10 | >10 |
| **11c** | H | $CF_3$ | H | 3.1 | >100 | — | >10 | >10 |
| **11d** | H | CN | H | 31.5 | 1.0 | 31.5 | 1.0 | 3.2 |
| **11e** | H | OMe | H | 31.5 | 31.5 | 1.0 | >10 | 3.5 |
| **11f** | H | OH | H | 3.5 | 10.0 | — | 0.3 | 0.32 |
| **11g** | OMe | H | H | >100 | 10.0 | >10 | 9.0 | >10 |
| **11h** | OH | H | H | >100 | >100 | — | 0.3 | 0.5 |
| **11i** | OMe | OMe | OMe | >100 | >100 | — | 7.0 | >10 |
| **11j** | H | F | H | 30.0 | 0.1 | 300 | >10 | 1.0 |
| **11k** | F | F | H | 3.1 | 0.5 | 6.2 | 0.4 | 3.2 |
| **16a** | OMe | OH | H | 1.1 | 30 | — | >10 | 0.1 |
| **16b** | OH | OMe | H | 1.0 | 3.2 | — | >10 | 0.3 |
| Luteolin | | | | — | — | — | — | 3.2 |
| Caffeic acid | | | | — | — | — | 3.0 | — |
| NDGA | | | | — | — | — | >10 | 3.5 |
| Rofecoxib | | | | >100 | 0.5 | >200 | — | — |

[a] Values are means of two determinations acquired using an ovine COX-1/COX-2 and potato 5-LOX/soyabean 15-LOX, assay kits (Catalog No. 560101, 60401, and 760700, Cayman Chemicals Inc., Ann Arbor, MI, USA) and the deviation from the mean is <10% of the mean value.
[b] In vitro COX-2 selectivity index (SI, COX-1 $IC_{50}$/COX-2 $IC_{50}$).

and LOX inhibitor with moderate COX-2 selectivity (COX-2 $IC_{50}$ = 1.0 μM; SI = 31.5) and a more potent inhibition of 5-LOX (5-LOX $IC_{50}$ = 1.0 μM; 15-LOX $IC_{50}$ = 3.2 μM), as shown in Table 1.[11] Introduction of a C-1 *p*-MeO-phenyl moiety (**11e**) provided moderate COX inhibition (COX-1/2 $IC_{50}$ = 31.5 μM), whereas incorporation of a C-1 *m*-MeO-phenyl substituent (**11g**) increased both COX-2 inhibitory potency and selectivity (COX-2 $IC_{50}$ = 10 μM; SI > 10) compared to the regioisomer **11e**. Compound **11g** also exhibited selective inhibition of 5-LOX (5-LOX $IC_{50}$ = 9.0 μM), relative to 15-LOX. The C-1 4-hydroxyphenyl compound **11f**, an equipotent inhibitor of 5- and 15-LOX (5-LOX $IC_{50}$ = 0.3 μM; 15-LOX $IC_{50}$ = 0.32 μM), was about a 9-fold more potent inhibitor of 5-LOX than the reference drug caffeic acid (5-LOX $IC_{50}$ = 3.0 μM). Incorporation of a C-1 3,4,5-trimethoxyphenyl substituent (**11i**, $R^1 = R^2 = R^3$ = OMe) led to a complete loss of COX inhibitory activity, but **11i** did exhibit selective inhibition of 5-LOX ($IC_{50}$ = 7.0 μM). Within this class of compounds, **11j** possessing a C-1 *p*-fluorophenyl substituent was 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). On the other hand, introduction of a C-1 difluorophenyl substituent (**11k**, $R^1 = R^2$ = F) decreased both COX-2 inhibitory potency and selectivity (COX-2 $IC_{50}$ = 0.5 μM; SI = 6.0), but increased 5-LOX inhibition (5-LOX $IC_{50}$ = 0.4 μM). Introduction of a methoxyphenol antioxidant moiety at the C-1 position provided compounds **16a** ($R^1$ = OMe, $R^2$ = OH) and **16b** ($R^1$ = OH, $R^2$ = OMe) that exhibited moderate COX-1 selectivity, with preferential inhibition of 15-LOX (Table 1). Compound **16a**, which exhibited potent inhibition of 15-LOX (15-LOX $IC_{50}$ = 0.1 μM), is 35-fold more potent than the reference drug NDGA (15-LOX $IC_{50}$ = 3.5 μM).

A molecular modeling (docking) experiment was carried out to investigate the binding interactions of the most selective and potent COX-2 inhibitor **11j** [1-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)prop-2-yn-1-one] within the COX-2 binding site (Fig. 1).[10,12] The most stable ligand–enzyme complex of **11j** (Fig. 1) showed that this ligand binds in the center of the COX-2 binding site such that the C-3 *p*-$MeSO_2$-phenyl substituent is positioned in the vicinity of the COX-2 secondary pocket where it is surrounded by Phe518, Arg513, Gln192, His90, Ser353, and Val523. One of the oxygen atoms of the $SO_2$Me group undergoes a hydrogen bonding interaction with the backbone N*H* of Phe518 (distance = 3.63 Å), whereas the other oxygen atom

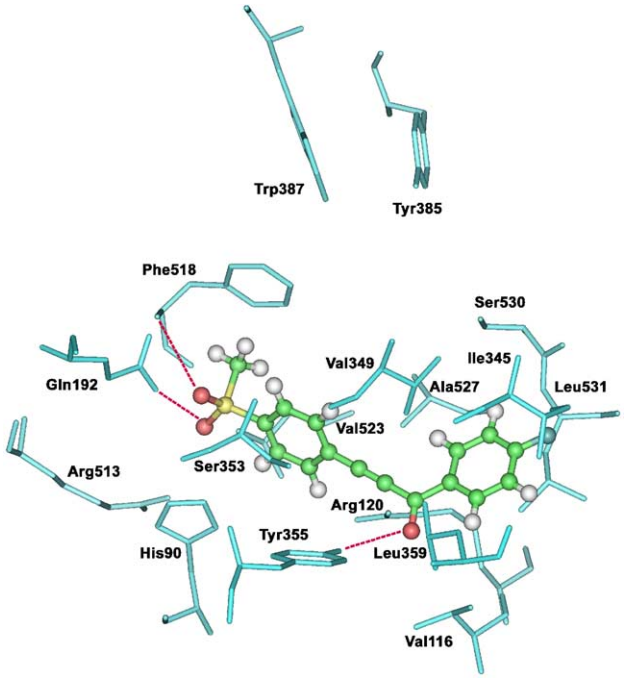



**Figure 1.** Docking of **11j** in the binding site of murine COX-2. Hydrogen atoms of the amino acid residues are not shown for clarity.

undergoes a favorable hydrogen bonding interaction with the N*H*$_2$ of Gln192 (distance = 2.70 Å). The methyl group of the *p*-$SO_2$Me moiety is within van der Waal's contact range (distance <4 Å) of the aromatic ring of Phe518. It is notable that, the prop-2-yn-1-one carbonyl oxygen atom (C≡C–C=*O*) is hydrogen bonding to the O*H* of Tyr355 close to the entrance of the COX-2 secondary pocket (distance = 2.01 Å) and it is positioned about 4.38 Å from the guanidine side chain (N*H*$_2$) of Arg120. The C-1 *p*-fluorophenyl substituent is oriented in a region comprised of Ala527, Ser530, Leu531, Leu359, Val349, and Ile345. The distance between the O*H* of Ser530 and fluorine atom of the *p*-fluorophenyl substituent was about 4.53 Å, and the fluorine atom is within van der Waal's contact range of the methyl side chain of Ile345 (distance <3.5 Å).

In summary, structure–activity studies show that (i) the 1,3-diphenylprop-2-yn-1-one structure is a suitable template to design dual inhibitors of COX and LOX; (ii) COX/LOX inhibition was sensitive to substituents present on the C-1 phenyl ring, with **11j** [1-(4-fluorophenyl)-3-(4-methanesulfonylphenyl)prop-2-yn-1-one] exhibiting potent and selective COX-2 inhibition (COX-2 $IC_{50}$ = 0.1 μM; SI = 300); and (iii) an optimal combination of COX and LOX inhibition was obtained for 1-(4-cyanophenyl)-3-(4-methanesulfonylphenyl)prop-2-yn-1-one (**11d**, COX-2 $IC_{50}$ = 1.0 μM; SI = 31.5; 5-LOX $IC_{50}$ = 1.0 μM; 15-LOX $IC_{50}$ = 3.2 μM). Further studies are in progress to extend these structure–activity data and to determine anti-inflammatory activity of potential lead compounds.

## Acknowledgments

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11. Analytical data for **11d**. Yield, 85%; white solid; mp 183–185 °C; IR (film): 2220 (C≡N), 2200 (C≡C), 1640 (C=O), 1311, 1150 ($SO_2$) $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 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. Calcd for $C_{17}H_{11}NO_3S$: C, 66.01; H, 3.58; N, 4.58. Found: C, 65.82; H, 3.44; N, 4.40.
12. Analytical data for **11j**. Yield, 81%; yellow solid; mp 142–144 °C; IR (film): 2200 (C≡C), 1647 (C=O), 1309, 1154 ($SO_2$) $cm^{-1}$; $^1$H NMR ($CDCl_3$): $\delta$ 3.10 (s, 3H, $SO_2CH_3$), 7.19 (dd, $^3J_{HH}$ = 8.5, $^3J_{FH}$ = 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, $^3J_{HH}$ = 8.5, $^4J_{FH}$ = 5.5 Hz, 2H, fluorophenyl H-2, H-6). Anal. Calcd for $C_{16}H_{11}FO_3S$: C, 63.57; H, 3.67. Found: C, 63.43; H, 3.47.