Design, Synthesis, and Structure−Activity Relationship Studies of 3,4,6-Triphenylpyran-2-ones as Selective Cyclooxygenase-2 Inhibitors

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A group of regioisomeric 3,4,6-triphenylpyran-2-ones with a $MeSO_2$ pharmacophore at the para-position of either a C-3 phenyl or a C-4 phenyl substituent on the central six-membered pyran-2-one ring were prepared and evaluated in vitro for their abilities to inhibit the isozymes COX-1 and COX-2. Structure−activity relationship (SAR) data, acquired by substituent modification at the para-position of the C-6 phenyl ring attached to the central pyranone, showed that 6-(4-methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (**12e**) was the most potent and selective COX-2 inhibitor (COX-2 $IC_{50} = 0.02$ μM; COX-1 $IC_{50} > 100$ μM) with a high COX-2 selectivity index (SI > 5000) relative to the reference drugs celecoxib (COX-2 $IC_{50} = 0.07$ μM; SI = 474) and rofecoxib (COX-2 $IC_{50} = 0.50$ μM; SI > 200). 6-(4-Methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (**12e**) was a more potent oral antiinflammatory agent ($ID_{50} = 5.6$ mg/kg) than celecoxib ($ID_{50} = 10.8$ mg/kg) in a carrageenan-induced rat paw edema assay. In a 4% NaCl-induced abdominal constriction assay, a 5 mg/kg oral dose of **12e** exhibited good analgesic activity at different time intervals producing 37.5 and 69% inhibition of writhing at 30 and 60 min, respectively. In contrast, the corresponding 6-(4-methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one regiosiomer (**12o**) was a less potent and selective COX-2 inhibitor (COX-2 $IC_{50} = 0.45$ μM; SI = 70). A molecular modeling study for **12e** indicated that the *p*-OMe substituent on the C-6 phenyl ring interacts with the COX-2 binding site amino acids Ile^{345}, Val^{349}, Leu^{359}, Leu^{531}, and Met^{535} and that the OMe substituent may be responsible for proper orientation of the C-3 *p*-SO_2Me-phenyl ring within the COX-2 secondary pocket (Gln^{192}, Arg^{513}, and Phe^{518}). These results show that the COX-2 selectivity and potency of 3,4,6-triphenylpyranone regioisomers can be modulated by appropriate placement of the *p*-SO_2Me pharmacophore on either the C-3 or C-4 phenyl moiety. In addition, electronic properties at the para-position of a C-6 phenyl substituent on the central pyranone ring govern COX-2 inhibitory potency and selectivity by controlling the orientation of the *p*-SO_2Me pharmacophore within the COX-2 secondary pocket.

Introduction

The discovery of another isoform of the enzyme cyclooxygenase (COX-2) in the early 1990s led to the development of a new class of nonsteroidal antiinflammatory drugs (NSAIDs) known as selective cyclooxygenase-2 (COX-2) inhibitors.[1−3] Recent studies have shown that selective COX-2 inhibitors are equally effective in the treatment of inflammatory diseases such as rheumatoid arthritis (RA) and osteoarthritis (OA) with an improved gastrointestinal (GI) profile compared to traditional NSAIDs.[4,5] In recent years there has been significant advancement in drug design concepts regarding selective COX-2 inhibitors and their potential application for the treatment of a variety of disease states. For example, the treatment of colon, breast, and prostate cancer have shown promising results.[6,7] In addition, recent studies have highlighted the potential application of selective COX-2 inhibitors in the prophylactic prevention of neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson's disease.[8,9]

Diarylheterocycles constitute a major class of selective COX-2 inhibitors. Extensive structure−activity relationship (SAR) studies for the diarylheterocycle class have shown that a SO_2NH_2 or SO_2Me substituent at the para-position of one of the aryl rings is a requirement for optimum COX-2 selectivity and potency.[10] Accordingly, the selective COX-2 inhibitor celecoxib (**1**) possesses a diarylheterocyclic ring template with a central five-membered pyrazole ring, whereas rofecoxib (**2**) has a central five-membered lactone [2(5*H*)-furanone] ring system.[11,12] Similarly, the recently launched selective COX-2 inhibitor valdecoxib (**3**) possesses a diarylheterocyclic ring template with a central five-membered isoxazole ring, whereas etoricoxib (**4**) possesses a central six-membered pyridine ring.[13−15]

Recent studies have shown that compounds possessing a pyran-2-one moiety are known to exhibit diverse biological activities including anticancer, antimicrobial, and HIV-protease inhibitory activities.[16−18] We have shown that a novel class of diarylheterocycle possessing a central pyran-2-one ring (**5**, see Chart 1) acts as a suitable template for the design of selective COX-2 inhibitors that exhibited good antiinflammatory and analgesic activity profiles.[19] In addition, other studies have also used a central pyran-2-one ring template for the design of selective COX-2 inhibitors.[20,21] As part of our ongoing research program, we describe herein the design, synthesis, and structure−activity relationship

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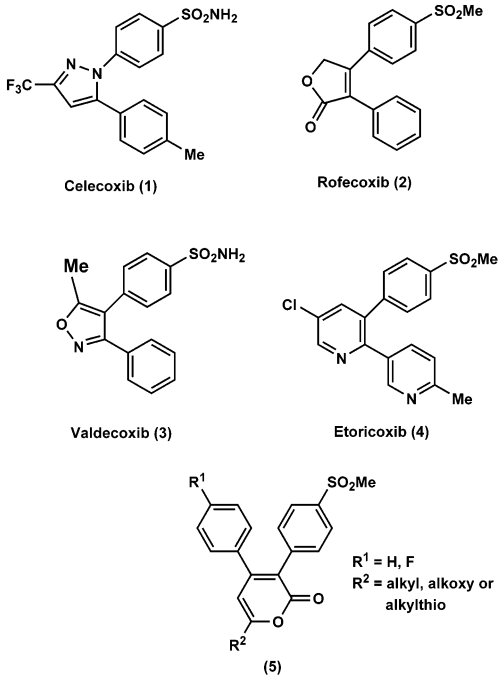
Chart 1. Representative Examples of Tricyclic Selective COX-2 Inhibitors



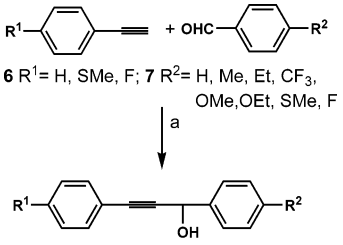
(SAR) studies for a novel class of regioisomeric, 3,4,6-triphenylpyran-2-ones as selective COX-2 inhibitors.

Chemistry

A number of methods for synthesizing 3,4,6-triphenylpyran-2-one derivatives have been reported.[22−24] The synthetic methods used to prepare the regioisomeric 3,4,6-triphenylpyran-2-ones (**12a**−**s**) are outlined in Schemes 1−3. The initial strategy was to synthesize the 1,3-diarylprop-2-yn-1-ols (**8a**−**r**), which was achieved by the condensation of a para-substituted-phenylacetylene (**6**) with a para-substituted-benzaldehyde (**7**) in the presence of *n*-butyllithium (44−84%).[25] Subsequent oxidation of **8a**−**r** using activated manganese dioxide (MnO_2) afforded the corresponding 1,3-diarylprop-2-yn-1-one (**9a**−**r**) in good yield (52−85%) as shown in Scheme 1. The 3,4,6-triphenylpyran-2-ones (**11a**−**s**) having a central six-membered lactone ring were obtained in moderate to good yields (22−62%) by condensation of a para-substituted-phenylacetic acid ester (**10a**−**c**) with a 1,3-diarylprop-2-yn-1-one (**9a**−**j** or **9l**−**r**) in the presence of a base such as sodium hydride at 25 °C (Scheme 2).[22] Oxidation of **11a**−**s**, using an aqueous solution of Oxone, afforded the regioisomeric title compounds **12a**−**s**, possessing a *p*-methanesulfonylphenyl substituent at either the C-3 or C-4 position of the central six-membered pyran-2-one in good yield (60−85%) as illustrated in Scheme 3. The 3,4,6-triphenylpyran-2-one derivatives (**12t** and **12u**) were synthesized in moderate yield (17−34%) by condensation of ethyl 4-methanesulfonylphenylacetate (**10d**) with a 1,3-diarylprop-2-yn-1-one (**9g** or **9k**) in the presence of the base potassium *tert*-butoxide (Scheme 4).

The 3,4,6-triphenylpyran-2-one **11t** with a C-6 *p*-NO_2-phenyl substituent was prepared by condensation of 1-(4-nitrophenyl)-3-phenylprop-2-yn-1-one (**9s**) with the phenylacetic acid ester **10b** in the presence of NaH. Subsequent oxidation of **11t** using aqueous Oxone

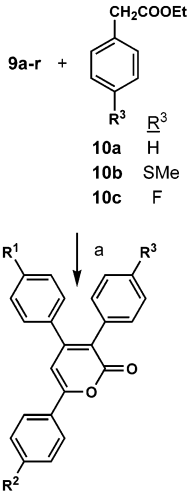
Scheme 1[a]



	R^1	R^2		R^1	R^2
9a	H	H	**9j**	F	OEt
9b	H	Me	**9k**	F	SMe
9c	H	Et	**9l**	SMe	H
9d	H	CF_3	**9m**	SMe	Me
9e	H	OMe	**9n**	SMe	Et
9f	H	OEt	**9o**	SMe	CF_3
9g	H	SMe	**9p**	SMe	OMe
9h	H	F	**9q**	SMe	OEt
9i	F	OMe	**9r**	SMe	F

[a] Reagents and conditions: (a) THF, −78 °C, *n*-BuLi, and then at −78 °C to 25 °C overnight; (b) acetone, MnO_2, 25 °C, 4−5 h.

Scheme 2[a]



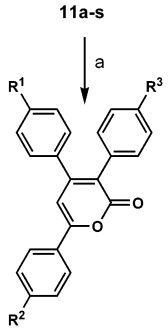
	R^3
10a	H
10b	SMe
10c	F

	R^1	R^2	R^3		R^1	R^2	R^3
11a	H	H	SMe	**11k**	SMe	H	H
11b	H	Me	SMe	**11l**	SMe	Me	H
11c	H	Et	SMe	**11m**	SMe	Et	H
11d	H	CF_3	SMe	**11n**	SMe	CF_3	H
11e	H	OMe	SMe	**11o**	SMe	OMe	H
11f	H	OEt	SMe	**11p**	SMe	OEt	H
11g	H	F	SMe	**11q**	SMe	F	H
11h	F	OMe	SMe	**11r**	SMe	OMe	F
11i	F	OEt	SMe	**11s**	SMe	OEt	F
11j	H	SMe	H				

[a] Reagents and conditions: (a) DMSO, NaH, 25 °C, 1 h.

afforded the methanesulfonyl derivative **12v** in good yield (76%). The 1,3-diarylprop-2-yn-1-one (**9s**) was prepared in low yield (25%) by a copper-catalyzed cross coupling of phenylacetylene with 4-nitrobenzoyl chloride in the presence of triethylamine as base (Scheme 5).[26] Reduction of the nitro compound **12v** using hydrazine hydrate in the presence of Pd/C afforded the amine

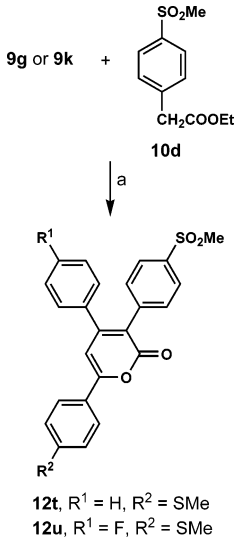
Scheme 3[a]



	R1	R2	R3		R1	R2	R3
12a	H	H	SO_2Me	**12k**	SO_2Me	H	H
12b	H	Me	SO_2Me	**12l**	SO_2Me	Me	H
12c	H	Et	SO_2Me	**12m**	SO_2Me	Et	H
12d	H	CF_3	SO_2Me	**12n**	SO_2Me	CF_3	H
12e	H	OMe	SO_2Me	**12o**	SO_2Me	OMe	H
12f	H	OEt	SO_2Me	**12p**	SO_2Me	OEt	H
12g	H	F	SO_2Me	**12q**	SO_2Me	F	H
12h	F	OMe	SO_2Me	**12r**	SO_2Me	OMe	F
12i	F	OEt	SO_2Me	**12s**	SO_2Me	OEt	F
12j	H	SO_2Me	H				

[a] Reagents and conditions: (a) 1,4-dioxane, aqueous Oxone, 25 °C, 4−5 h.

Scheme 4[a]

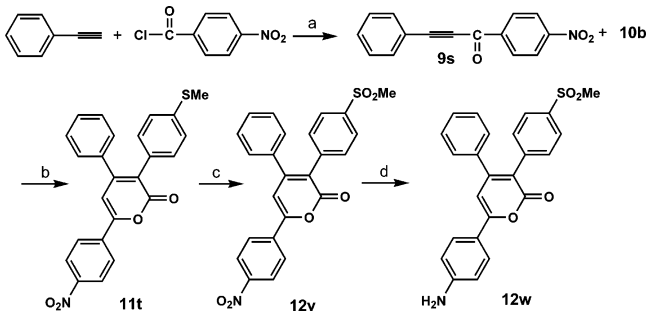


[a] Reagents and conditions: (a) *tert*-butyl alcohol, potassium *tert*-butoxide, 50−60 °C, 1−1.5 h.

derivative **12w** in good yield (76%).[27] *O*-Demethylation of the C-6 methoxyphenyl compound **12e** using neat pyridinium chloride at 190−210 °C afforded the corresponding phenol derivative **12x** in low yield (20%) as shown in Scheme 6.[28]

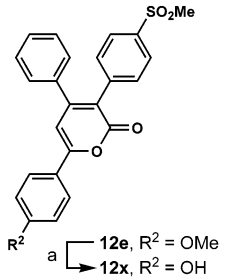
The C-4 4-methanesulfonylphenyl regioisomer **12y** of the C-3 4-methanesulfonlyphenyl compound **12t** was prepared using the reaction sequence shown in Scheme 7. Thus, the 1,3-diarylprop-2-yn-1-one derivative (**9t**) was synthesized by condensation of 1-ethynyl-4-methanesulfonylbenzene with 4-methylthiobenzaldehyde in the presence of *n*-BuLi to afford the 1,3-diarylprop-2-yn-1-ol (**8s**) which was subsequently oxidized to the corresponding ketone **9t** using activated MnO_2 in good yield (67%). The starting material 1-ethynyl-4-methanesulfonylbenzene was prepared by the oxidation of 1-ethynyl-4-methanesulfanylbenzene using aqueous Ox-

Scheme 5[a]



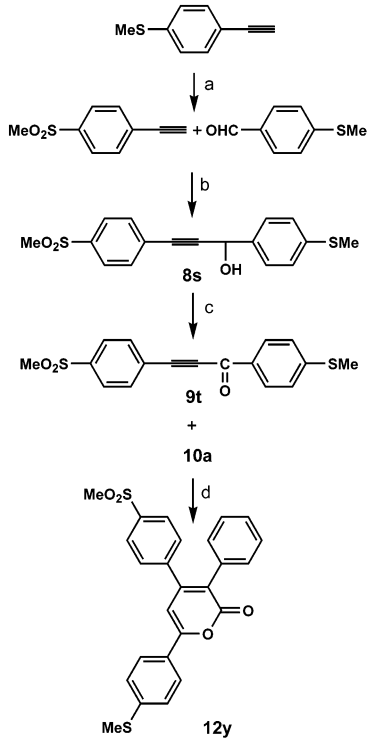
[a] Reagents and conditions: (a) Et_3N, CuI, 25 °C, 30 h (b) DMSO, NaH, 25 °C, 1 h; (c) 1,4-dioxane, aqueous Oxone, 25 °C, 4−5 h; (d) ethanol (95%), Pd/C, $NH_2NH_2{\cdot}H_2O$, 75−78 °C, 1 h.

Scheme 6[a]



[a] Reagents and conditions: (a) pyridinium hydrochloride, 190−210 °C, 1−1.5 h.

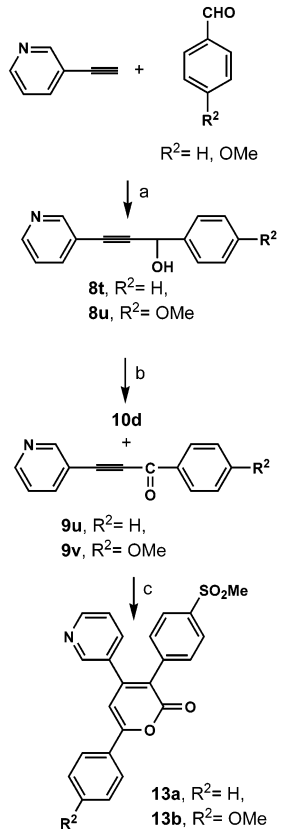
Scheme 7[a]



[a] Reagents and conditions: (a) 1,4-dioxane, aqueous Oxone, 25 °C, 4−5 h; (b) THF, −78 °C, *n*-BuLi, −78 °C to 25 °C overnight; (c) acetone, MnO_2, 25 °C, 4−5 h; (d) *tert*-butyl alcohol, potassium *tert*-butoxide, 50−60 °C, 1−1.5 h.

one solution (Scheme 7). The final cyclization reaction was carried out by condensation of **9t** with ethyl phenylacetate (**10a**) in the presence of potassium *tert*-butoxide to afford the target product **12y** in good yield (46%).

Scheme 8[a]

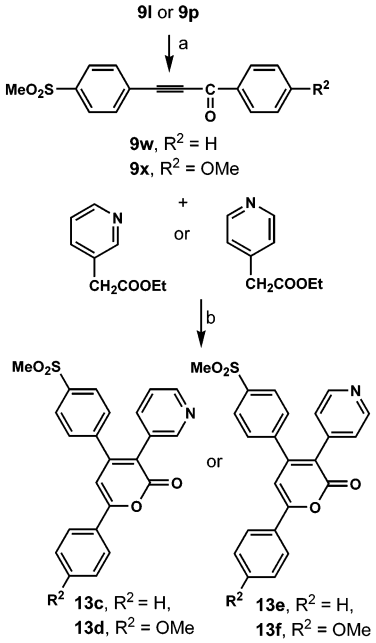


[a] Reagents and conditions: (a) THF, −78 °C, *n*-BuLi, −78 °C to 25 °C overnight; (b) acetone, MnO_2, 25 °C, 4−5 h; (c) CH_2Cl_2, NaH, 25 °C, 1 h.

The diphenylpyran-2-ones (**13a**−**f**), possessing a pyridyl substituent at either the C-3 or C-4 position, were prepared by the condensation of a 1,3-diarylprop-2-yn-1-one (**9u**−**x**) with a phenyl (pyridyl) acetic acid ester in the presence of a base as illustrated in Schemes 8 and 9. Accordingly, reaction of 3-ethynylpyridine with a para-substituted-benzaldehyde (R^2 = H or OMe) in the presence of *n*-BuLi afforded the alcohol **8t** or **8u** in good yield (40−53%), which on subsequent oxidation with activated MnO_2 afforded the respective ketone **9u** or **9v** (57−61%). The C-4 pyridin-3-ylpyran-2-ones (**13a** and **13b)** were synthesized by the condensation of acetylenic ketones **9u** and **9v** with ethyl 4-methanesulfonylphenyl acetate (**10d**) in the presence of NaH in 24−46% yield as shown in Scheme 8. The acetylenic ketones **9l** and **9p** possessing a methylthio moiety were oxidized to the corresponding acetylenic ketones **9w** and **9x** possessing a *p*-SO_2Me substituent using aqueous Oxone solution. Condensation of **9w** or **9x** with a pyridin-3-yl or pyridin-4-ylacetic acid ester in the presence of NaH afforded the respective C-3 pyridin-3-yl or pyridin-4-ylpyran-2-one (**13c**−**f**) in 22−42% yield as shown in Scheme 9.

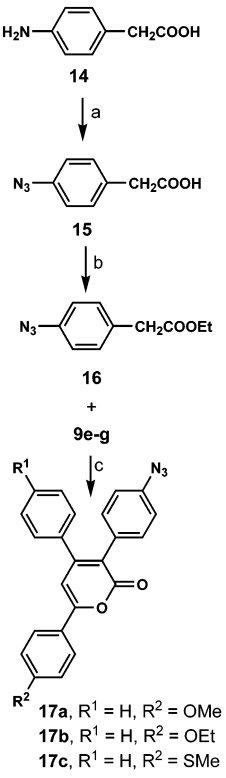
A small group of 3,4,6-triphenylpyran-2-ones in which the SO_2Me pharmacophore was replaced by a dipolar azido substituent (**17a**−**c**) were prepared as shown in Scheme 10. Accordingly, the reaction of 4-aminophenylacetic acid (**14**) with sodium nitrite under acidic conditions in the presence of sodium azide afforded 4-azidophenylacetic acid (**15**) in high yield (94%). Subsequent

Scheme 9[a]



[a] Reagents and conditions: (a) 1,4-dioxane, aqueous Oxone, 25 °C, 4−5 h; (b) CH_2Cl_2, NaH, 25 °C, 1 h.

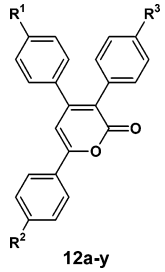
Scheme 10[a]



[a] Reagents and conditions: (a) $NaNO_2$, concentrated HCl, 0 °C, 15 min, NaN_3, 15−20 min, 25 °C; (b) concentrated H_2SO_4, ethanol (95%), 70−75 °C, 3−4 h; (c) CH_2Cl_2, NaH, 25 °C, 1 h.

esterification of **15** using 95% ethanol under acidic conditions afforded the corresponding ester **16** in good yield (87%). Condensation of the respective acetylenic ketones (**9e**−**g**) with 4-azidophenylacetic acid ester (**16**) in the presence of NaH afforded the title compounds (**17a**−**c**) in moderate yield (30−35%) as shown in Scheme 10.

Table 1. COX-1/COX-2 Inhibitory Activities of the 3,4,6-Triphenylpyran-2-ones (**12a**−**y**)



12a-y

compd	R^1	R^2	R^3	IC_{50} (μM)[a] COX-1	IC_{50} (μM)[a] COX-2	selectivity[b] index (SI)
12a	H	H	SO_2Me	>100	>100	–
12b	H	Me	SO_2Me	>100	>100	–
12c	H	Et	SO_2Me	>100	>100	–
12d	H	CF_3	SO_2Me	>100	>100	–
12e	H	OMe	SO_2Me	>100	0.02	>5000
12f	H	OEt	SO_2Me	>100	0.05	>2000
12g	H	F	SO_2Me	>100	5.1	>19
12h	F	OMe	SO_2Me	20	1.16	17
12i	F	OEt	SO_2Me	3.2	158	–
12j	H	SO_2Me	H	>100	>100	–
12k	SO_2Me	H	H	>100	1.3	>77
12l	SO_2Me	Me	H	>100	1.2	>83
12m	SO_2Me	Et	H	>100	1.4	71
12n	SO_2Me	CF_3	H	25.3	3.2	8
12o	SO_2Me	OMe	H	31.5	0.45	70
12p	SO_2Me	OEt	H	31.6	1.1	29
12q	SO_2Me	F	H	11.0	0.07	157
12r	SO_2Me	OMe	F	10.7	1.3	8
12s	SO_2Me	OEt	F	1.07	14.50	–
12t	H	SMe	SO_2Me	37.7	0.16	236
12u	F	SMe	SO_2Me	>100	31.6	3
12v	H	NO_2	SO_2Me	>100	7.0	
12w	H	NH_2	SO_2Me	32.5	0.8	
12x	H	OH	SO_2Me	>100	>100	–
12y	SO_2Me	SMe	H	31.2	4.5	7
Celecoxib				33.1	0.07	474
Rofecoxib				>100	0.50	>200

[a] Values are means of two determinations and deviation from the mean is < 10% of the mean value (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI). [b] In vitro COX-2 selectivity index (IC_{50} COX-1/IC_{50} COX-2).

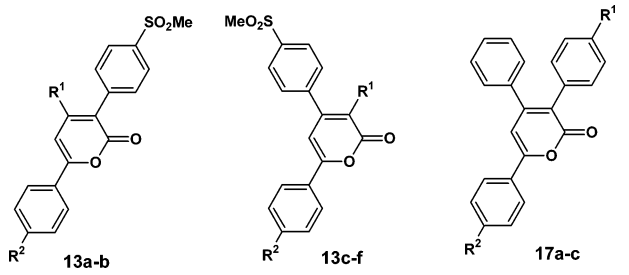
Results and Discussion

A group of regioisomeric 3,4,6-triphenylpyran-2-ones (**12a**−**y**, **13a**−**f**, and **17a**−**c**) were designed such that the COX-2 SO_2Me pharmacophore was located at the para-position of either the C-3 or the C-4 phenyl substituent on the central pyran-2-one ring. In addition, the substituent at the para-position of the C-6 phenyl ring was varied (H, Me, Et, CF_3, OMe, OEt, F, SMe) to determine the effect of steric and electronic substituent properties on COX-2 inhibitory potency and selectivity. Structure−activity relationship (SAR) data for the title compounds (IC_{50} values) were acquired by evaluating their in vitro ability to inhibit the COX-1 and COX-2 isozymes.[19] In this regard, the pyran-2-one compounds (**12a**−**i** and **12t**−**x**) possessing a C-3 *p*-methanesulfonylphenyl substituent on the central lactone ring exhibited a broad range of COX-2 inhibitory potencies and selectivity [IC_{50} values > 100 (inactive) to 0.02 (very potent) μM range] as summarized in Table 1. Varying the R^2-substituent at the para-position of the C-6 phenyl substituent on the central pyran-2-one had a dramatic effect on COX-2 inhibitory potency and selectivity where the C-6 *p*-methoxyphenyl compound **12e**, which exhibited excellent COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.02 μM; SI > 5000), was 3.5- and 25-fold more potent than celecoxib (COX-2 IC_{50} = 0.07 μM; SI = 474) and rofecoxib (COX-2 IC_{50} = 0.50 μM; SI > 200), respectively. Insertion of a *p*-OEt substituent (**12f**) resulted in a modest decrease in COX-2 inhibitory potency (COX-2 IC_{50} = 0.05 μM). Compound **12t** possessing an electron donating R^2-thiomethyl substituent at the para-position of the C-6 phenyl substituent exhibited weaker COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.16 μM; COX-1 IC_{50} = 37.7 μM; SI = 236), compared to the R^2-OMe (**12e**) and R^2-OEt (**12f**) compounds. Introduction of a fluorine substituent at the para-position on the C-4 phenyl ring (**12h**, **12i**, and **12u)** generally decreased COX-2 inhibitory potency and selectivity (Table 1). The relative COX-2 inhibitory potency order for this group of pyran-2-ones (**12a**−**i** and **12t**−**x**) was OMe > OEt > SMe > NH_2 > F > NO_2 > inactive H, Me, Et, CF_3, and OH.

The C-6 *p*-methanesulfonylphenyl regioisomer **12j** (R^2 = $MeSO_2$) was an inactive COX inhibitor (COX-1 and COX-2 IC_{50} > 100 μM). The C-4 *p*-methanesulfonylphenyl pyran-2-one regioisomers (**12k**−**s**, **12y**) exhibited moderate to good COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.07−31.6 μM range) as illustrated in Table 1. The C-4 *p*-methanesulfonylphenyl regioisomer **12o,** which possesses a C-6 *p*-methoxyphenyl substituent, also exhibited good COX-2 inhibitory potency (COX-2 IC_{50} = 0.45 μM; SI = 70) although it is less potent and selective than the corresponding C-3 *p*-methanesulfonylphenyl regioisomer **12e**. Introduction of a R^3-F substituent at the para-position of a C-3 phenyl ring significantly decreased both COX-2 inhibitory potency and selectivity (**12r** and **12s**). In contrast, the C-6 *p*-fluorophenyl compound **12q** was a highly potent COX-2 inhibitor (COX-2 IC_{50} = 0.07 μM; SI = 157) as shown in Table 1. In general, for the C-4 *p*-methanesulfonylphenyl group of compounds (**12k**−**s** and **12y**), introduction of a R^2-H, Me, Et or OEt substituent at the para-position of the C-6 phenyl ring provided compounds that are equipotent inhibitors of COX-2. Replacement of the C-3 or C-4 phenyl moieties of 3,4,6-triphenylpyran-2-ones by a corresponding pyridin-3-yl or pyridin-4-yl substituent significantly altered the COX-2 inhibitory potency and selectivity (Table 2). In this sub group, 3-(pyridin-4-yl) compound (**13f**) exhibited the best combination of COX-2 inhibitory potency and selectivity (COX-2 IC_{50} = 0.32 μM; SI > 312).

The SO_2NH_2 and the SO_2Me pharmacophores present in celecoxib and rofecoxib respectively, are known to induce COX-2 selectivity by insertion into the secondary pocket of the COX-2 binding site that is absent in COX-1.[10] This secondary-pocket in COX-2 is formed due to a conformational change at Tyr^{355} that is attributed to the presence of Ile^{523} in COX-1 relative to Val^{523} having a smaller side chain in COX-2.[29] It has been reported that replacement of His^{513} in COX-1 by Arg^{513} in COX-2 plays a key role in the hydrogen-bond network of the COX-2 binding site.[30] Recently we exploited, for the first time, the amino acid Arg^{513} to design selective COX-2 inhibitors having a dipolar azide (N_3) pharmacophore that can undergo an electrostatic (ion−ion) interaction with Arg^{513} in the COX-2 secondary-pocket.[27] Accordingly, we replaced the SO_2Me pharmacophore in the most potent and selective COX-2 inhibitors identified from the 3,4,6-

Table 2. COX-1/COX-2 Inhibitory Activities of 3,4,6-Triphenylpyran-2-ones (**13a**−**f** and **17a**−**c**)



compd	R^1	R^2	IC_{50} (μM)[a] COX-1	IC_{50} (μM)[a] COX-2	selectivity[b] index (SI)
13a	pyridin-3-yl	H	3.0	8.0	< 0.4
13b	pyridin-3-yl	OMe	0.44	0.03	15
13c	pyridin-3-yl	H	3.2	0.33	10
13d	pyridin-3-yl	OMe	0.15	1.6	−
13e	pyridin-4-yl	H	>100	3.0	>33
13f	pyridin-4-yl	OMe	>100	0.32	>312
17a	N_3	OMe	>100	0.5	>200
17b	N_3	OEt	>100	2.3	43
17c	N_3	SMe	30.0	0.38	79
Celecoxib			33.1	0.07	474
Rofecoxib			>100	0.5	>200

[a] Values are means of two determinations and deviation from the mean is <10% of the mean value (Catalog No. 560101, Cayman Chemicals Inc., Ann Arbor, MI). [b] In vitro COX-2 selectivity index (IC_{50} COX-1/IC_{50} COX-2).

triphenylpyran-2-ones investigated in this study (**12e, 12f** and **12t**) with a dipolar azido bioisostere to evaluate compounds **17a**−**c** (see Table 2). It is biologically relevant that compounds possessing a dipolar *p*-N_3 pharmacophore on the C-3 phenyl substituent (**17a**−**c**) retained their COX-2 selectivity, even though they are less potent (COX-2 IC_{50} = 0.38−2.3 μM range; SI = 79 to > 200 range) than the corresponding C-3 *p*-$MeSO_2$-phenyl analogues.

The orientation and binding interactions of the potent and selective COX-2 inhibitor **12e** [6-(4-methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one] within the COX-2 active site was investigated by a molecular modeling (docking) experiment (Figure 1). The C-3 *p*-methanesulfonylphenyl regioisomer **12e** binds in the center of the COX-2 binding site such that the SO_2Me pharmacophore inserts deep into the COX-2 secondary pocket, and the *p*-methanesulfonylphenyl moiety of the ligand which undergoes hydrophobic contact with the protein is surrounded by Phe^{518}, Arg^{513}, Gln^{192}, Ser^{353}, Leu^{352}, and Val^{523}. Due to the presence of a less bulky Val^{523} in COX-2, relative to Ile^{523} in COX-1, the S-atom of the SO_2Me substituent is positioned about 4.53 Å inside the entrance to the COX-2 secondary pocket with one of its oxygen atoms forming a hydrogen bond with the N*H* of Phe^{518} (distance = 2.19 Å). The distance between the other SO_2Me oxygen atom and the NH_2 (guanidino group) of Arg^{513} is about 3.71 Å. The C-4 unsubstituted phenyl ring was oriented toward a hydrophobic pocket composed of Trp^{387}, Tyr^{385}, Leu^{384}, and Tyr^{348} at the top of the COX-2 binding site. The distance between the center of the C-4 phenyl ring and *O*H of Ser^{530} was about 6.15 Å. The central six-membered lactone (pyran-2-one) ring was located near the mouth of the COX-2 binding site such that the central C=*O* of the lactone ring undergoes a weak hydrogen bonding interaction with the O*H* of Ser^{353} (distance = 2.91 Å).

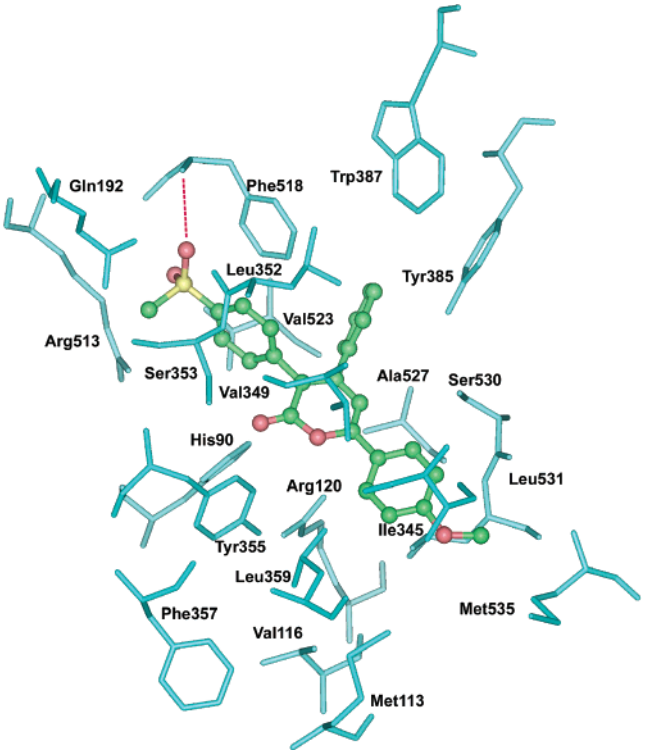


Figure 1. Docking 6-(4-methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (**12e**) (ball-and-stick) in the active site of murine COX-2 ($E_{intermolecular}$ = −90.14 kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

The interspacial distance between the O*H* of Tyr^{355} and C=*O* is about 5.11 Å, and the *O*-atom of the central lactone ring is positioned about 3.26 Å from the NH_2 (guanidino group) of Arg^{120}.

The C-6 *p*-methoxyphenyl substituent of **12e** is oriented toward a hydrophobic pocket close to the mouth of the COX-2 active site such that it is within a van der Waal's contact range (distance ≈ 5 Å) of Ala^{527}, Ser^{530}, Leu^{531}, Met^{535}, Ile^{345}, Val^{349}, and Leu^{359}. The distance between the center of the C-6 phenyl ring and the *O*H of Ser^{530} was about 4.86 Å. The phenyl ring (of the C-6 *p*-MeO-phenyl substituent) undergoes a cation−π interaction with the NH_2 of the guanidino side chain of Arg^{120} (distance = 6.0 Å). This interaction may confer important COX-2 selectivity implications by disrupting the salt bridge between Arg^{120} and Glu^{524} at the mouth of the COX-2 binding site.[29,31] Interestingly, the *p*-OMe substituent attached to the C-6 phenyl ring is within a van der Waal's contact range of Met^{535} (distance ≈ 5 Å), and the OMe group interacts favorably with the SMe side chain of Met^{535}.

A similar docking study for the C-4 *p*-$MeSO_2$-phenyl regioisomer **12o** in the COX-2 binding site shows that the C-4 *p*-methanesulfonylphenyl moiety is positioned in the vicinity of amino acid residues (Phe^{518}, Arg^{513}, and Gln^{192}) lining the COX-2 secondary pocket as shown in Figure 2. Unlike the C-3 regioisomer **12e**, the *O*-atom of the SO_2Me group in **12o** is not hydrogen bonded to Phe^{518} (distance = 3.10 Å), and the methanesulfonyl S-atom is located about 3.8 Å inside the entrance to the COX-2 secondary pocket (Val^{523}). Similar to the C-3 regioisomer **12e**, the C-3 unsubstituted-phenyl ring in **12o** is oriented toward a hydrophobic pocket made up

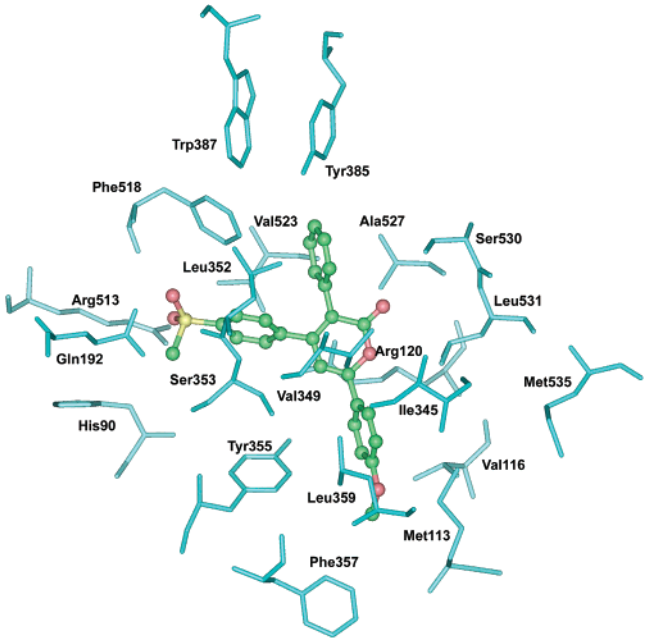


Figure 2. Docking 6-(4-methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (**12o**) (ball-and-stick) in the active site of murine COX-2 ($E_{\text{intermolecular}} = -84.44$ kcal/mol). Hydrogen atoms are not shown for clarity.

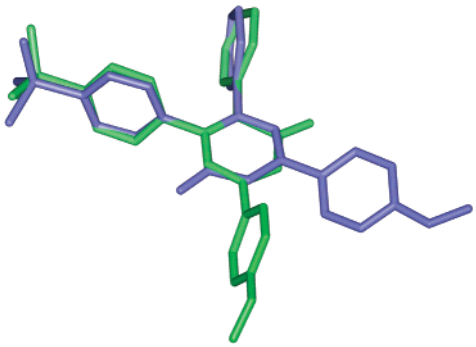


Figure 3. Overlay of the binding modes of **12e** (blue) and **12o** (green) within the active site of murine COX-2. Hydrogen atoms are not shown for clarity.

of Trp,[387] Tyr[385], and Tyr[348]. The C=*O* of the central lactone ring is about 4.33 Å away from the O*H* of Ser[530]. The C-6 *p*-MeO-phenyl moiety of **12o** is located near the mouth of the COX-2 binding site, and it is surrounded by amino acid residues Met[113], Val[116], Arg[120], Val[349], Tyr[355], Phe[357], and Leu[359], and the OMe substituent is much further removed from Met[535] compared to the C-3 *p*-MeSO$_2$-phenyl regioisomer **12e**.

Conformational comparisons of the binding modes of the two regioisomers **12e** and **12o** in the COX-2 active site are shown in Figure 3. The root-mean-square deviation (RMSD) between these two conformations was ~0.04 Å. The atom pairs of the vicinal diaryl system were selected for superimposition of **12e** and **12o** (the lactone C-3, C-4 and the aromatic carbons C-1, C′-1). The vicinal aromatic rings of both **12e** and **12o**, and also their *p*-sulfonyl group, lie in a common plane. However, the SO$_2$Me group of **12e** extends much deeper inside the COX-2 secondary pocket relative to **12o** (the S-atom of the SO$_2$Me substituent of **12e** is positioned about 4.53 Å inside the entrance to the COX-2 secondary pocket unlike **12o**). The central six-membered pyran-2-one ring

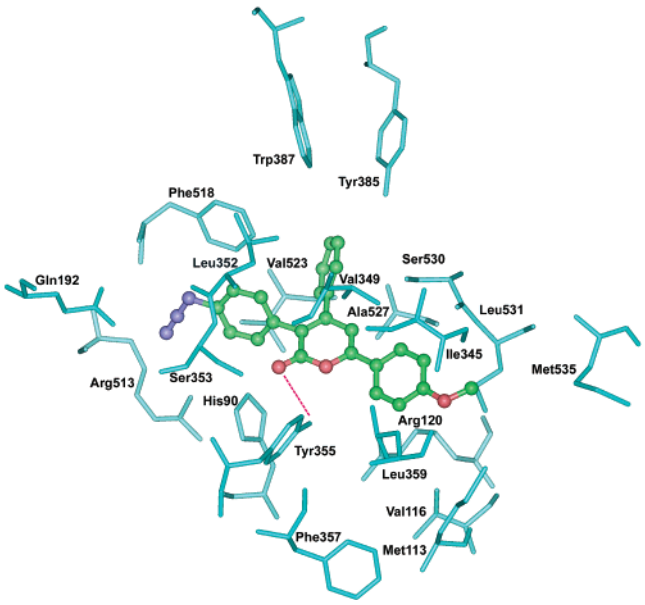


Figure 4. Docking 6-(4-methoxyphenyl)-3-(4-azidophenyl)-4-phenylpyran-2-one (**17a**) (ball-and-stick) in the active site of murine COX-2 ($E_{\text{intermolecular}} = -77.48$ kcal/mol). Red dotted line represents hydrogen bonding. Hydrogen atoms are not shown for clarity.

of both **12e** and **12o** lie in a common plane. It is noteworthy that due to the regioisomeric position of the SO$_2$Me group, on either the C-3 or C-4 phenyl ring of the central lactone ring, the C=O is either close to Tyr[355] (in **12e**) at the entrance to COX-2 secondary pocket or near Ser[530] (in **12o**) within the COX-2 binding site. Recent studies have shown the important interaction of diarylheterocyclic selective COX-2 inhibitors with Tyr[355].[32] In addition, the C-6 *p*-MeO-phenyl substituent in the two regioisomers is positioned in different regions within the COX-2 binding site. In this regard, interaction of the *p*-MeO-phenyl ring substituent of **12e** within a hydrophobic pocket comprised of Ile[345], Val[349], Leu[359], and Met[535] appears to orient the C-3 *p*-MeSO$_2$-phenyl substituent deeper into the COX-2 secondary pocket which does not occur in the case of the C-4 *p*-MeSO$_2$-phenyl regioisomer **12o**. A series of molecular dynamics (MD) simulations on the stabilities of the enzyme−ligand complexes reveal that **12e** ($E_{\text{intermolecular}} = -90.14$ kcal/mol) has a higher binding affinity for COX-2 as compared to **12o** ($E_{\text{intermolecular}} = -84.44$ kcal/mol). These data is consistent with the more potent COX-2 inhibition exhibited by **12e** (COX-2 IC$_{50}$ = 0.02; SI > 5000) as compared to **12o** (COX-2 IC$_{50}$ = 0.45; SI = 70).

The binding mode of the pyran-2-one **17a**, in which the COX-2 SO$_2$Me pharmacophore was replaced by a linear azido (N$_3$) bioisostere, within the COX-2 active site is similar to that of the respective C-3 *p*-MeSO$_2$-phenyl analogue **12e**, although there are some subtle differences (Figure 4). As expected, the linear dipolar azido substituent of the C-3 *p*-N$_3$-phenyl moiety is oriented toward the COX-2 secondary pocket with the dipolar N$_3$ group participating in favourable interactions (electrostatic) with Arg[513] and Phe[518].[27] The terminal *N*-atom of the dipolar azide group is located about 3.23 Å inside the COX-2 secondary pocket (Val[523]) and about 2.63 Å removed from the N*H*$_2$ (guanidino group) of Arg[513] (ion−ion interaction). The terminal *N*-atom can also undergo a favorable interaction with the backbone

N*H* of Phe[518] (distance = 3.81 Å). In addition, the terminal *N*-atom of the dipolar azide group is nearly 4.65 Å from the N*H* of His[90] at the entrance to the COX-2 secondary pocket. The C-4 unsubstituted phenyl ring is located near a hydrophobic pocket comprised of Trp[387], Tyr[385], and Leu[384] observed similar to the related SO_2Me analogue **12e**. The central C=*O* of the lactone ring is hydrogen bonded to the O*H* of Tyr[355] (distance = 2.50 Å) at the mouth of the COX-2 binding site. The C-6 *p*-MeO-phenyl ring is within van der Waal's contact range (distance = 5 Å) with the protein, and it is surrounded by Ile[345], Leu[531], Leu[359], and Met[535]. The C-6 phenyl ring also undergoes a cation−π interaction with the NH_2 of the guanidino side chain of Arg[120] (distance = 6.13 Å). These observations show that the dipolar azido pharmacophore serves as a suitable bioisostere that undergoes electrostatic interaction with Arg[513] within the COX-2 secondary pocket. Accordingly, COX-2 selectivity is retained for compounds belonging to the 3,4,6-triphenylpyran-2-one class by replacing the traditional SO_2Me pharmacophore by a linear dipolar azido substituent (**17a**, COX-2 IC_{50} = 0.50; SI > 200).

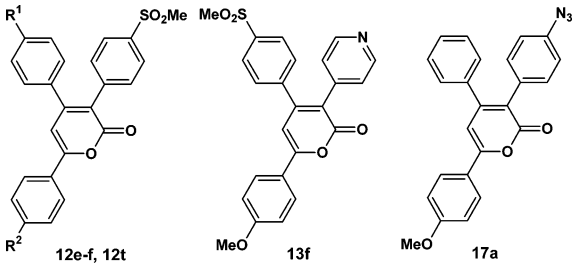
Our previous study on C-3 *p*-methanesulfonylphenyl pyranones indicated that C-6 alkyl-, alkoxy-, or alkylthio- substituents are a major determinant of COX-2 inhibitory potency and selectivity due to their ability to orient the central pyranone ring such that the C-3 *p*-SO_2Me pharmacophore is positioned in the vicinity of the COX-2 secondary pocket.[19] In this study on 3,4,6-triphenylpyranones, it is shown that a C-6 para-substituted phenyl ring also plays a critical role in positioning the *p*-SO_2Me pharmacophore close to the COX-2 secondary pocket. In addition, it appears that the regioisomeric placement of the *p*-SO_2Me pharmacophore at either the C-3 or C-4 phenyl ring in this latter group of C-6 phenyl analogues is an important determinant with respect to COX-2 inhibitory potency and selectivity. In this regard, the C-3 *p*-SO_2Me-substituted pyranones (**12e**, **12f**, and **12t**) exhibited superior COX-2 inhibitory potency and selectivity.

Pharmacological studies were carried out to assess the in vivo antiinflammatory and analgesic activity of some of the most potent and selective COX-2 inhibitors (**12e**, **12f, 12t, 13f**, and **17a**) based on in vitro enzyme inhibition data (Table 3). In a carrageenan-induced rat paw edema assay model, **12e** (COX-2 IC_{50} = 0.02; SI > 5000) exhibited a 31% inhibition of inflammation at 3 h after administration of a 5 mg/kg oral dose. The most active oral antiinflammatory compound **12f** (COX-2 IC_{50} = 0.05; SI > 2000) that exhibited an ID_{50} of 5.6 mg/kg was more potent than the reference drug celecoxib (ID_{50} = 10.8 mg/kg). In a rat model 4% NaCl-induced abdominal constriction assay, a 5 mg/kg po dose of these pyran-2-ones exhibited good analgesic activities (37−75% range) at 30 or 60 min postdrug administration. The 6-(4-ethoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (**12f**) exhibited good analgesic activity where a 5 mg/kg po dose reduced writhing by 58 and 75% at 30 and 60 min postdrug administration.

Conclusions

The SAR data acquired for this class of 3,4,6-triphenylpyran-2-ones have shown that (i) compounds exhibiting high COX-2 inhibitory potency and selectivity can be designed by appropriate placement of a *p*-SO_2Me pharmacophore on either a C-3 or C-4 phenyl ring, in which the pyran-2-one ring serves as a suitable central ring template, (ii) docking studies revealed that the C-3 *p*-$MeSO_2$-phenyl regioisomer having an appropriately substituted C-6 phenyl ring, exhibit better binding affinity than the corresponding C-4 *p*-$MeSO_2$-phenyl regioisomer, (iii) COX-2 inhibitory potency and selectivity is sensitive to substituent electronic properties at the para-position of the C-6 phenyl ring where the C-6 *p*-MeO-phenyl compound **12e** exhibits the best combination of potency and selectivity, and (iv) the linear azido (N_3) substituent is a suitable bioisostere to replace a traditional SO_2Me COX-2 pharmacophore.

Table 3. Antiinflammatory and Analgesic Activities of 3,4,6-Triphenylpyran-2-ones (**12e**,**f**, **12t**, **13f**, and **17a**)



			AI activity[a]	analgesic activity[b]	
compd	R^1	R^2	% inhibition at 3 h	% inhibition at 30 min	% inhibition at 60 min
12e	H	OMe	31.0 ± 4.7[c]	37.5 ± 14.4	69.0 ± 14.0
12f	H	OEt	61.3 ± 1.2[d]	58.3 ± 10.2	75.0 ± 17.6
12t	H	SMe	52.6 ± 1.6[e]	72.0 ± 12.3	64.7 ± 19.4
13f			50.3 ± 8.0[f,g]	58.3 ± 8.3	55.0 ± 9.1
17a			42.3 ± 7.6[h]	47.2 ± 10.0	55.5 ± 13.6
Ibuprofen			56.2 ± 2.0[i]	−	−
Celecoxib			80.0 ± 2.0[j,k]	69.33 ± 12.1	79.5 ± 2.0

[a] Inhibitory activity in a carrageenan-induced rat paw edema assay. The results are expressed as mean ± SEM (n = 4−6) following a 5 mg/kg oral dose of the test compound. [b] Inhibitory activity in the rat 4% NaCl-induced abdominal constriction assay. The results are expressed as mean ± SEM (n = 4−6) following a 5 mg/kg oral dose of the test compound. [c] ID_{50} = 19.2 mg/kg oral dose. [d] ID_{50} = 5.6 mg/kg oral dose. [e] ID_{50} = 7.9 mg/kg oral dose. [f] ID_{50} = 21.4 mg/kg oral dose. [g] 30 mg/kg oral dose. [h] ID_{50} = 5.6 mg/kg oral dose. [i] 50 mg/kg oral dose. [j] 50 mg/kg oral dose. [k] ID_{50} = 10.8 mg/kg oral dose.

Experimental Section

General. Melting points were determined using a Buchi capillary apparatus and are uncorrected. Ibuprofen was purchased from Sigma (St. Louis, MO). All other reagents including **8a** (1,3-diphenylprop-2-yn-1-ol) and **9a** (1,3-diphenylprop-2-yn-1-one) 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, ^{13}C 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). ^{13}C NMR spectra were acquired using the J modulated spin−echo technique where methyl and methine carbons appear as positive peaks and methylene and quaternary carbon resonances appear as negative peaks. 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[11,12] Compounds **8b** [1-(4-methylphenyl)-3-phenylprop-2-yn-1-ol], **8e** [1-(4-methoxylphenyl)-3-phenylprop-2-yn-1-ol], **8h** [1-(4-fluorophenyl)-3-phenylprop-2-yn-1-ol], **9b** [1-(4-methylphenyl)-3-phenylprop-2-yn-1-one], **9e** [1-(4-methoxyphenyl)-3-phenylprop-2-yn-1-one], and 1-ethynyl-4-methanesulfonylbenzene and the phenylacetic acid esters (**10b** and **10c**) were prepared according to the previously reported methods.[33−37] Male Sprague−Dawley rats, used in the antinflammatory-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.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ols (8c−r). A 4-substituted-phenylacetylene (**6**, R^1 = H, SMe or F; 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 4-substituted-benzaldehyde (**7**, R^2 = H, Me, Et, CF_3, OMe, OEt, SMe, or F; 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 after stirring and warming to room temperature. The reaction mixture was washed with saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (2 × 20 mL), the organic phase was separated and 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 **8c−r** in 44−84% yield. Some physical and spectroscopic data for **8c−r** are listed below.

1-(4-Ethylphenyl)-3-phenylprop-2-yn-1-ol (8c). The product was obtained as a white solid (1.4 g, 61%): mp 108−110 °C; IR (film): 3315 (OH), 2193 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.22 (d, J = 5.8 Hz, 1H, CHO*H*), 2.63 (q, J = 7.3 Hz, 2H, CH_2CH_3), 5.66 (d, J = 5.8 Hz, 1H, C*H*OH), 7.23 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.28−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.42−7.49 (m, 2H, phenyl H-2, H-6), 7.52 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{17}H_{16}O$): C, H.

1-(4-Trifluoromethylphenyl)-3-phenylprop-2-yn-1-ol (8d). The product was obtained as a pale yellow oil (1.5 g, 59%): IR (film): 3313 (OH), 2183 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (d, J = 5.8 Hz, 1H, CHO*H*), 5.64 (d, J = 5.8 Hz, 1H, C*H*OH), 7.30−7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.44−7.49 (m, 2H, phenyl H-2, H-6), 7.66 (d, J = 8.2 Hz, 2H, 4-trifluorophenyl H-2, H-6), 7.74 (d, J = 8.2 Hz, 2H, 4-trifluorophenyl H-3, H-5).

1-(4-Ethoxyphenyl)-3-phenylprop-2-yn-1-ol (8f). The product was obtained as a pale yellow oil (1.6 g, 65%): IR (film): 3310 (OH), 2188 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, J = 7.3 Hz, 3H, OCH_2CH_3), 2.19 (d, J = 5.8 Hz, 1H, CHO*H*), 4.07 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 5.64 (d, J = 5.8 Hz, 1H, C*H*OH), 6.91 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.30−7.45 (m, 3H, phenyl H-3, H-4, H-5), 7.47−7.51 (m, 2H, phenyl H-2, H-6), 7.53 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{17}H_{16}O_2$): C, H.

1-(4-Methylsulfanylphenyl)-3-phenylprop-2-yn-1-ol (8g). The product was obtained as a pale yellow solid (1.95 g, 74.5%): mp 56−58 °C; IR (film): 3310 (OH), 2188 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.24 (d, J = 5.8 Hz, 1H, CHO*H*), 2.50 (s, 3H, SCH_3), 5.60 (d, J = 5.8 Hz, 1H, C*H*OH), 7.28 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.32−7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.44−7.49 (m, 2H, phenyl H-2, H-6), 7.53 (d, J = 8.2 Hz, 2H, 4-methanesulfanylphenyl H-2, H-6). Anal. ($C_{16}H_{14}OS$): C, H.

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (8i). The product was obtained as an oil (2.11 g, 84.4%): IR (film): 3320 (OH), 2124 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.19 (d, J = 5.8 Hz, 1H, CHO*H*), 3.87 (s, 3H, OCH_3), 5.63 (d, J = 5.8 Hz, 1H, C*H*OH), 6.96 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.00 (dd, J^3_{HH} = 8.2, J^3_{FH} = 8.2 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.43 (dd, J^3_{HH} = 8.2, J^4_{FH} = 4.9 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.52 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{16}H_{13}FO_2$): C, H.

3-(4-Fluorophenyl)-1-(4-ethoxyphenyl)prop-2-yn-1-ol (8j). The product was obtained as an oil (2.06 g, 77.7%): IR (film): 3374 (OH), 2120 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.41 (t, J = 7.3 Hz, 3H, OCH_2CH_3), 2.16 (d, J = 5.8 Hz, 1H, CHO*H*), 4.07 (q, J = 7.3 Hz, 2H, OCH_2CH_3), 5.62 (d, J = 5.8 Hz, 1H, C*H*OH), 6.90 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 6.97 (dd, J^3_{HH} = 8.2, J^3_{FH} = 8.2 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.42 (dd, J^3_{HH} = 8.2, J^4_{FH} = 4.9 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.51 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{17}H_{15}FO_2$): C, H.

3-(4-Fluorophenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-ol (8k). The product was obtained as an oil (1.78 g, 67.2%): IR (film): 3347 (OH), 2135 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.22 (d, J = 5.8 Hz, 1H, CHO*H*), 2.50 (s, 3H, SCH_3), 5.64 (d, J = 5.8 Hz, 1H, C*H*OH), 6.98 (dd, J^3_{HH} = 8.2, J^3_{FH} = 8.2 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.25 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.41 (dd, J^3_{HH} = 8.2, J^4_{FH} = 4.9 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.51 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{16}H_{13}FOS$): C, H.

3-(4-Methylsulfanylphenyl)-1-phenylprop-2-yn-1-ol (8l). The product was obtained as a reddish brown oil (1.98 g, 80%): IR (film): 3335 (OH), 2226 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.26 (d, J = 6.1 Hz, 1H, CHO*H*), 2.48 (s, 3H, SCH_3), 5.68 (d, J = 6.1 Hz, 1H, C*H*OH), 7.16 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.32 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.36−7.44 (m, 3H, phenyl H-3, H-4, H-5), 7.60−7.63 (m, 2H, phenyl H-2, H-6). Anal. ($C_{16}H_{14}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methylphenyl)prop-2-yn-1-ol (8m). The product was obtained as an oil (1.63 g, 62.2%): IR (film): 3351 (OH), 2220 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.19 (d, J = 5.8 Hz, 1H, CHO*H*), 2.38 (s, 3H, CH_3), 2.49 (s, 3H, SCH_3), 5.65 (d, J = 5.8 Hz, 1H, C*H*OH), 7.16 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.21 (d, J = 8.0 Hz, 2H, 4-methylphenyl H-3, H-5), 7.37 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.40 (d, J = 8.0 Hz, 2H, 4-methylphenyl H-2, H-6). Anal. ($C_{17}H_{16}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-ethylphenyl)prop-2-yn-1-ol (8n). The product was obtained as an oil (1.96 g, 71.2%): IR (film): 3324 (OH), 2193 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.18 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 2.53 (q, J = 7.6 Hz, 2H, CH_2CH_3), 5.65 (d, J = 6.1 Hz, 1H, C*H*OH), 7.15 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.17 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.52 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{18}H_{18}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-trifluoromethylphenyl)prop-2-yn-1-ol (8o). The product was obtained as an oil (1.35 g, 43%): IR (film): 3355 (OH), 2227 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.40 (d, J = 5.8 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 5.74 (d, J = 5.8 Hz, 1H, C*H*OH), 7.17 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.36 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.66 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6), 7.73 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5). Anal. ($C_{17}H_{13}F_3OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ol (8p). The product was obtained as an oil (2.32 g, 83.7%): IR (film): 3351 (OH), 2220 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.17 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 3.81 (s, 3H, OCH_3), 5.64 (d, J = 6.1 Hz, 1H, C*H*OH), 6.92 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.16 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.53 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{17}H_{16}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-ethoxyphenyl)prop-2-yn-1-ol (8q). The product was obtained as a dark brown oil (2.14 g, 73.5%): IR (film): 3328 (OH), 2206 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.17 (d, J = 5.8 Hz, 1H, CHO*H*), 2.49 (s, 3H, SCH_3), 4.02 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 5.65 (d, J = 5.8 Hz, 1H, C*H*OH), 6.91 (d,

J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.16 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.51 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{18}H_{18}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-fluorophenyl)prop-2-yn-1-ol (8r). The product was obtained as an oil (1.96 g, 73.8%): IR (film): 3382 (OH), 2220 (C≡C) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.28 (d, J = 6.1 Hz, 1H, CHO*H*), 2.49 (s, 3H, SC*H*$_3$), 5.66 (d, J = 6.1 Hz, 1H, C*H*OH), 7.09 (dd, J^3_{HH} = 8.8, J^3_{FH} = 8.8 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.17 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.36 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.56 (dd, J^3_{HH} = 8.8, J^4_{FH} = 5.5 Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{16}H_{13}FOS$): C, H.

General Procedure for the Synthesis of 1,3-Diarylprop-2-yn-1-ones (9c−r). To a stirred solution of the respective 1,3-diarylprop-2-yn-1-ol (**8c−r**; 4.5 mmol) in acetone (25 mL) was added activated manganese(IV) oxide (7.8 g, 90 mmol), the reaction mixture was stirred for 4−5 h at 25 °C after which MnO_2 was filtered off, and the organic solvent was removed in vacuo to give the title compound (**9c−r**) in good yield (52−85%). Some physical and spectroscopic data for **9c−r** are listed below.

1-(4-Ethylphenyl)-3-phenylprop-2-yn-1-one (9c). The product was obtained as a oil by the oxidation of **8c** in the presence of MnO_2 (0.74 g, 70.2%): IR (film): 2152 (C≡C), 1650 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.25 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.71 (q, J = 7.3 Hz, 2H, CH_2CH_3), 7.33 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.35−7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.67−7.69 (m, 2H, phenyl H-2, H-6), 8.13 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{17}H_{14}O$): C, H.

1-(4-Trifluoromethylphenyl)-3-phenylprop-2-yn-1-one (9d). The product was obtained as a white solid by the oxidation of **8d** in the presence of MnO_2 (0.96 g, 77.8%): mp 70−72 °C; IR (film): 2150 (C≡C), 1649 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.43−7.56 (m, 3H, phenyl H-3, H-4, H-5), 7.67−7.73 (m, 2H, phenyl H-2, H-6), 7.79 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5), 8.33 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6). Anal. ($C_{16}H_9F_3O$): C, H.

1-(4-Ethoxyphenyl)-3-phenylprop-2-yn-1-one (9f). The product was obtained as a white solid by the oxidation of **8f** in the presence of MnO_2 (1.3 g, 53%): mp 57−59 °C; IR (film): 2152 (C≡C), 1645 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.49 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.11 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.90 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.39−7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.67−7.69 (m, 2H, phenyl H-2, H-6), 8.18 (d, J = 8.5 Hz, 2H, 4-ethoxyphenyl H-2, H-6).

1-(4-Methylsulfanylphenyl)-3-phenylprop-2-yn-1-one (9g). The product was obtained as a solid by the oxidation of **8g** in the presence of MnO_2 (0.95 g, 83.6%): mp 50−51 °C; IR (film): 2172 (C≡C), 1642 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, SC*H*$_3$), 7.31 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.40−7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.61−7.67 (m, 2H, phenyl H-2, H-6), 8.11 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{16}H_{12}OS$): C, H.

1-(4-Fluorophenyl)-3-phenylprop-2-yn-1-one (9h). The product was obtained as a solid by the oxidation of **8h** in the presence of MnO_2 (1.4 g, 63%): mp 61−63 °C; IR (film): 2200 (C≡C), 1649 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.16 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.40−7.50 (m, 3H, phenyl H-3, H-4, H-5), 7.67−7.70 (m, 2H, phenyl H-2, H-6), 8.26 (dd, J^3_{HH} = 8.5, J^4_{FH} = 4.9 Hz, 2H, 4-fluorophenyl H-2, H-6).

3-(4-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (9i). The product was obtained as a solid by the oxidation of **8i** in the presence of MnO_2 (0.61 g, 53.3%): mp 104−106 °C; IR (film): 2193 (C≡C), 1632 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.90 (s, 3H, OC*H*$_3$), 6.98 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.00 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.43 (dd, J^3_{HH} = 8.5, J^4_{FH} = 4.9 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.52 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{16}H_{11}FO_2$): C, H.

3-(4-Fluorophenyl)-1-(4-ethoxyphenyl)prop-2-yn-1-one (9j). The product was obtained as a solid by the oxidation of **8j** in the presence of MnO_2 (0.68 g, 56.5%): mp 81−83 °C; IR (film): 2193 (C≡C), 1622 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.07 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.96 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.09 (dd, J^3_{HH} = 8.8, J^3_{FH} = 8.8 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.65 (dd, J^3_{HH} = 8.8, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 8.16 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{17}H_{13}FO_2$): C, H.

3-(4-Fluorophenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-one (9k). The product was obtained as a solid by the oxidation of **8k** in the presence of MnO_2 (0.76 g, 62.4%): mp 119−121 °C; IR (film): 2206 (C≡C), 1635 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.53 (s, 3H, SC*H*$_3$), 7.13 (dd, J^3_{HH} = 8.2, J^3_{FH} = 8.2 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.33 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.66 (dd, J^3_{HH} = 8.2, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 8.10 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{16}H_{11}FOS$): C, H.

3-(4-Methylsulfanylphenyl)-1-phenylprop-2-yn-1-one (9l). The product was obtained as a solid by the oxidation of **8l** in the presence of MnO_2 (0.77 g, 68%): mp 54−55 °C; IR (film): 2200 (C≡C), 1629 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, SC*H*$_3$), 7.23 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.50 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.54−7.66 (m, 3H, phenyl H-3, H-4, H-5), 8.20−8.23 (m, 2H, phenyl H-2, H-6). Anal. ($C_{16}H_{12}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methylphenyl)prop-2-yn-1-one (9m). The product was obtained as an oil by the oxidation of **8m** in the presence of MnO_2 (0.66 g, 55%): IR (film): 2186 (C≡C), 1616 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.38 (s, 3H, C*H*$_3$), 2.53 (s, 3H, SC*H*$_3$), 7.24 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.30 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-3, H-5), 7.58 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 8.10 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-2, H-6). Anal. ($C_{17}H_{14}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-ethylphenyl)prop-2-yn-1-one (9n). The product was obtained as a solid by the oxidation of **8n** in the presence of MnO_2 (0.62 g, 49%): mp 45−46 °C; IR (film): 2193 (C≡C), 1635 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.53 (s, 3H, SC*H*$_3$), 2.71 (q, J = 7.6 Hz, 2H, CH_2CH_3), 7.17 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.24 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.58 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 8.12 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{18}H_{16}OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-trifluoromethylphenyl)prop-2-yn-1-one (9o). The product was obtained as a solid by the oxidation of **8o** in the presence of MnO_2 (0.82 g, 57.2%): mp 88−90 °C; IR (film): 2220 (C≡C), 1636 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.54 (s, 3H, SC*H*$_3$), 7.26 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.59 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.78 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5), 8.31 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6). Anal. ($C_{17}H_{11}F_3OS$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (9p). The product was obtained as a solid by the oxidation of **8p** in the presence of MnO_2 (0.86 g, 67.8%): mp 80−82 °C; IR (film): 2200 (C≡C), 1618 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.52 (s, 3H, SC*H*$_3$), 3.88 (s, 3H, OC*H*$_3$), 6.97 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.23 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.56 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 8.17 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{17}H_{14}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-ethoxyphenyl)prop-2-yn-1-one (9q). The product was obtained as a oil by the oxidation of **8q** in the presence of MnO_2 (0.97 g, 67.5%): IR (film): 2220 (C≡C), 1636 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.47 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.53 (s, 3H, SC*H*$_3$), 4.10 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.96 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.23 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.57 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 8.16 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{18}H_{16}O_2S$): C, H.

3-(4-Methylsulfanylphenyl)-1-(4-fluorophenyl)prop-2-yn-1-one (9r). The product was obtained as a solid by the oxidation of **8r** in the presence of MnO_2 (0.54 g, 44.7%): mp 99−100 °C; IR (film): 2193 (C≡C), 1630 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 7.16 (dd, $J^3_{HH} = 8.8$, $J^3_{FH} = 8.8$ Hz, 2H, 4-fluorophenyl H-3, H-5), 7.26 (d, $J = 8.5$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.57 (d, $J = 8.5$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 8.20 (dd, $J^3_{HH} = 8.8$, $J^4_{FH} = 5.5$ Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{16}H_{11}FOS$): C, H.

General Procedure for the Synthesis of 3,4,6-Triphenylpyran-2-ones (11a−s). To a stirred solution of the ethyl 4-substituted-phenylacetate (**10a**−**c**, R^3 = H, SMe or F; 1.7 mmol) in DMSO (10 mL) was added NaH (95% dry powder, 1.9 mmol) immediately after which the respective 1,3-diarylprop-2-yn-1-one (**9a**−**r**, 1.7 mmol) in DMSO (10 mL) was added slowly. The reaction mixture was stirred at 25 °C for 1 h after which it was washed with 1 N HCl (10 mL) and extracted with EtOAc (2 × 20 mL), the organic phase was separated and dried over Na_2SO_4, and the organic portion was evaporated in vacuo. The brownish oil obtained was purified by silica gel column chromatography using hexanes−ethyl acetate (1:2, v/v or 1:3, v/v) as eluent to afford the respective title compound **11a**−**s** in 22−62% yield. Some physical and spectroscopic data for **11a**−**s** are listed below.

3-(4-Methylsulfanylphenyl)-4,6-diphenylpyran-2-one (11a). The product was obtained as a yellow solid by condensation of **9a** with **10b** in the presence of NaH (0.34 g, 55%): mp 232−234 °C; IR (film): 1703 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, SCH_3), 6.84 (s, 1H, pyranone H-5), 7.09 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.12 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.18−7.21 (m, 2H, phenyl H-2, H-6), 7.29−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.47−7.49 (m, 3H, phenyl H-3, H-4, H-5), 7.89−7.93 (m, 2H, phenyl H-2, H-6). Anal. ($C_{24}H_{18}O_2S$): C, H.

6-(4-Methylphenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11b). The product was obtained as a yellow solid by condensation of **9b** with **10b** in the presence of NaH (0.18 g, 28.3%): mp 246−248 °C; IR (film): 1705 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.45 (s, 3H, SCH_3), 6.79 (s, 1H, pyranone H-5), 7.08 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.11 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.15−7.17 (m, 2H, phenyl H-2, H-6), 7.20−7.23 (m, 3H, phenyl H-3, H-4, H-5), 7.28 (d, $J = 8.5$ Hz, 2H, 4-methylphenyl H-3, H-5), 7.79 (d, $J = 8.5$ Hz, 2H, 4-methylphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_2S$): C, H.

6-(4-Ethylphenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11c). The product was obtained as a yellow solid by condensation of **9c** with **10b** in the presence of NaH (0.23 g, 34.5%): mp 216−217 °C; IR (film): 1709 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.28 (t, $J = 7.6$ Hz, 3H, CH_2CH_3), 2.45 (s, 3H, SCH_3), 2.68 (q, $J = 7.6$ Hz, 2H, CH_2CH$_3$), 6.80 (s, 1H, pyranone H-5), 7.08 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.12 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.14−7.20 (m, 2H, phenyl H-2, H-6), 7.23−7.26 (m, 3H, phenyl H-3, H-4, H-5), 7.28 (d, $J = 8.2$ Hz, 2H, 4-ethylphenyl H-3, H-5), 7.81 (d, $J = 8.2$ Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{26}H_{22}O_2S$): C, H.

6-(4-Trifluoromethylphenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11d). The product was obtained as a yellow oil by condensation of **9d** with **10b** in the presence of NaH (0.22 g, 30.3%): IR (film): 1735 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 6.91 (s, 1H, pyranone H-5), 7.09 (d, $J = 8.8$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.13 (d, $J = 8.8$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.19−7.21 (m, 2H, phenyl H-2, H-6), 7.26−7.32 (m, 3H, phenyl H-3, H-4, H-5), 7.72 (d, $J = 8.2$ Hz, 2H, 4-trifluoromethylphenyl H-2, H-6), 8.0 (d, $J = 8.2$ Hz, 2H, 4-trifluoromethylphenyl H-3, H-5). Anal. ($C_{25}H_{17}F_3O_2S$): C, H.

6-(4-Methoxyphenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11e). The product was obtained as a oil by condensation of **9e** with **10b** in the presence of NaH (0.23 g, 34.4%): IR (film): 1703 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 6.72 (s, 1H, pyranone H-5), 6.97 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.09 (d, $J = 8.0$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.11 (d, $J = 8.0$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.16−7.18 (m, 2H, phenyl H-2, H-6), 7.20−7.23 (m, 3H, phenyl H-3, H-4, H-5), 7.85 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_3S$): C, H.

6-(4-Ethoxyphenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11f). The product was obtained as a yellow solid by condensation of **9f** with **10b** in the presence of NaH (0.15 g, 22.2%): mp 212−213 °C; IR (film): 1709 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3), 2.45 (s, 3H, SCH_3), 4.10 (q, $J = 7.0$ Hz, 2H, OCH_2CH$_3$), 6.72 (s, 1H, pyranone H-5), 6.95 (d, $J = 8.8$ Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.11 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.13 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.16−7.20 (m, 2H, phenyl H-2, H-6), 7.23−7.30 (m, 3H, phenyl H-3, H-4, H-5), 7.83 (d, $J = 8.8$ Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{26}H_{22}O_3S$): C, H.

6-(4-Fluorophenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11g). The product was obtained as a yellow solid by condensation of **9h** with **10b** in the presence of NaH (0.28 g, 43.3%): mp 235−237 °C; IR (film): 1703 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, SCH_3), 6.77 (s, 1H, pyranone H-5), 7.09 (d, $J = 8.8$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.12 (d, $J = 8.8$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.14 (dd, $J^3_{HH} = 8.2$, $J^3_{FH} = 8.2$ Hz, 2H, 4-fluorophenyl H-3, H-5), 7.18−7.20 (m, 2H, phenyl H-2, H-6), 7.25−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.88 (dd, $J^3_{HH} = 8.2$, $J^4_{FH} = 4.9$ Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{24}H_{17}FO_2S$): C, H.

6-(4-Methoxyphenyl)-3-(4-methylsulfanylphenyl)-4-(4-fluorophenyl)pyran-2-one (11h). The product was obtained as a yellow solid by condensation of **9i** with **10b** in the presence of NaH (0.40 g, 57%): mp 196−198 °C; IR (film): 1712 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 6.68 (s, 1H, pyranone H-5), 6.95 (dd, $J^3_{HH} = 8.4$, $J^3_{FH} = 8.4$ Hz, 2H, 4-fluorophenyl H-3, H-5), 6.97 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.08 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.11 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.13 (dd, $J^3_{HH} = 8.4$, $J^4_{FH} = 5.2$ Hz, 2H, 4-fluorophenyl H-2, H-6), 7.84 (d, $J = 8.8$ Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{25}H_{19}FO_3S$): C, H.

6-(4-Ethoxyphenyl)-3-(4-methylsulfanylphenyl)-4-(4-fluorophenyl)pyran-2-one (11i). The product was obtained as a yellowish oil by condensation of **9j** with **10b** in the presence of NaH (0.33 g, 44.8%): IR (film): 1698 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (t, $J = 7.0$ Hz, 3H, OCH$_2$CH_3), 2.46 (s, 3H, SCH_3), 3.99 (q, $J = 7.0$ Hz, 2H, OCH_2CH$_3$), 6.60 (s, 1H, pyranone H-5), 6.85 (dd, $J^3_{HH} = 8.4$, $J^3_{FH} = 8.4$ Hz, 2H, 4-fluorophenyl H-3, H-5), 6.90 (d, $J = 8.8$ Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.03 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.09 (d, $J = 9.0$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.10 (dd, $J^3_{HH} = 8.4$, $J^4_{FH} = 5.2$ Hz, 2H, 4-fluorophenyl H-2, H-6), 7.75 (d, $J = 8.8$ Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{26}H_{21}FO_3S$): C, H.

6-(4-Methylsulfanylphenyl)-3,4-diphenylpyran-2-one (11j). The product was obtained as a yellow solid by condensation of **9g** with **10a** in the presence of NaH (0.28 g, 45%): mp 170−172 °C; IR (film): 1708 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (s, 3H, SCH_3), 6.80 (s, 1H, pyranone H-5), 7.15−7.27 (m, 10H, phenyl H-2, H-3, H-4, H-5, H-6), 7.28 (d, $J = 8.5$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.81 (d, $J = 8.5$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{24}H_{18}O_2S$): C, H.

4-(4-Methylsulfanylphenyl)-3,6-diphenylpyran-2-one (11k). The product was obtained as a yellow solid by condensation of **9l** with **10a** in the presence of NaH (0.33 g, 52.5%): mp 177−179 °C; IR (film): 1709 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.45 (s, 3H, SCH_3), 6.83 (s, 1H, pyranone H-5), 7.07 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.09 (d, $J = 8.2$ Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.20−7.29 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.47−7.49 (m, 3H, phenyl H-3, H-4, H-5), 7.89−7.93 (m, 2H, phenyl H-2, H-6). Anal. ($C_{24}H_{18}O_2S$): C, H.

6-(4-Methylphenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11l). The product was obtained as a yellow solid by condensation of **9m** with **10a** in the presence of NaH (0.27 g, 41.5%): mp 150−152 °C; IR (film): 1709 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.46 (s, 3H, SCH_3), 6.78 (s, 1H, pyranone H-5), 7.08 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.12 (d, J = 8.0 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.14−7.20 (m, 2H, phenyl H-2, H-6), 7.23−7.26 (m, 3H, phenyl H-3, H-4, H-5), 7.28 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-3, H-5), 7.79 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_2S$): C, H.

6-(4-Ethylphenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11m). The product was obtained as a solid by condensation of **9n** with **10a** in the presence of NaH (0.30 g, 44.8%): mp 128−130 °C; IR (film): 1709 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.46 (s, 3H, SCH_3), 2.68 (q, J = 7.6 Hz, 2H, CH_2CH_3), 6.78 (s, 1H, pyranone H-5), 7.06 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.10 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.19−7.26 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.29 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.81 (d, J = 8.2 Hz, 2H, 4-ethylphenyl H-2, H-6). Anal. ($C_{26}H_{22}O_2S$): C, H.

6-(4-Trifluoromethylphenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11n). The product was obtained as a yellow oil by condensation of **9o** with **10a** in the presence of NaH (0.39 g, 52.3%): IR (film): 1703 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.47 (s, 3H, SCH_3), 6.90 (s, 1H, pyranone H-5), 7.08 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.13 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.20−7.30 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.73 (d, J = 8.5 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6), 8.01 (d, J = 8.5 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5). Anal. ($C_{25}H_{17}F_3O_2S$): C, H.

6-(4-Methoxyphenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11o). The product was obtained as a yellow solid by condensation of **9p** with **10a** in the presence of NaH (0.25 g, 37.7%): mp 156−158 °C; IR (film): 1710 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 3.88 (s, 3H, OCH_3), 6.71 (s, 1H, pyranone H-5), 6.97 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.08 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.11 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.19−7.32 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.85 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_3S$): C, H.

6-(4-Ethoxyphenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11p). The product was obtained as a yellow solid by condensation of **9q** with **10a** in the presence of NaH (0.44 g, 62.4%): mp 152−154 °C; IR (film): 1712 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.46 (s, 3H, SCH_3), 4.07 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.70 (s, 1H, pyranone H-5), 6.95 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.09 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.11 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.19−7.29 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.83 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{26}H_{22}O_3S$): C, H.

6-(4-Fluorophenyl)-4-(4-methylsulfanylphenyl)-3-phenylpyran-2-one (11q). The product was obtained as a yellow solid by condensation of **9r** with **10a** in the presence of NaH (0.26 g, 39.4%): mp 93−95 °C; IR (film): 1708 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 6.75 (s, 1H, pyranone H-5), 7.09 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.12 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.14 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.19−7.30 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.88 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{24}H_{17}FO_2S$): C, H.

6-(4-Methoxyphenyl)-4-(4-methylsulfanylphenyl)-3-(4-fluorophenyl)pyran-2-one (11r). The product was obtained as a yellow solid by condensation of **9p** with **10c** in the presence of NaH (0.40 g, 56%): mp 156−158 °C; IR (film): 1712 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 3.87 (s, 3H, OCH_3), 6.70 (s, 1H, pyranone H-5), 6.91−7.00 (m, 4H, fluorophenyl H-3, H-5; 4-methoxyphenyl H-3, H-5), 7.05 (d, J = 9.0 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.08 (d, J = 9.0 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.13 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.84 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6). Anal. ($C_{25}H_{19}FO_3S$): C, H.

6-(4-Ethoxyphenyl)-4-(4-methylsulfanylphenyl)-3-(4-fluorophenyl)pyran-2-one (11s). The product was obtained as a yellow solid by condensation of **9q** with **10c** in the presence of NaH (0.36 g, 49.4%): mp 160−162 °C; IR (film): 1698 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.43 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.47 (s, 3H, SCH_3), 4.07 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.69 (s, 1H, pyranone H-5), 6.92−7.01 (m, 4H, fluorophenyl H-3, H-5; 4-ethoxyphenyl H-3, H-5), 7.05 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.08 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.11 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.83 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6). Anal. ($C_{26}H_{21}FO_3S$): C, H.

General Procedure for the Synthesis of 3,4,6-Triphenylpyran-2-ones (12a−s). An aqueous solution of Oxone (50% w/v, 1.62 mmol) was added dropwise to a stirred solution of a 3,4,6-triphenylpyran-2-one (**11a**−**s**, 0.54 mmol) possessing a 4-methylsulfanylphenyl substituent on either the C-3, C-4, or C-6 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) and 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 and 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 hexanes−ethyl acetate (1:2, v/v or 1:3, v/v) as eluent to afford the respective title compound **12a**−**s** in 60−85% yield. Some physical and spectroscopic data for **12a**−**s** are listed below.

3-(4-Methanesulfonylphenyl)-4,6-diphenylpyran-2-one (12a). The product was obtained as a yellow solid by oxidation of **11a** in the presence of aqueous Oxone solution (0.14 g, 65%): mp 278−280 °C; IR (film): 1709 (C═O), 1306, 1152 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 6.89 (s, 1H, pyranone H-5), 7.12−7.16 (m, 2H, phenyl H-2, H-6), 7.28−7.37 (m, 3H, phenyl H-3, H-4, H-5), 7.40 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.44−7.51 (m, 3H, phenyl H-3, H-4, H-5), 7.82 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.90−7.93 (m, 2H, phenyl H-2, H-6). Anal. ($C_{24}H_{18}O_4S$): C, H.

6-(4-Methylphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12b). The product was obtained as a yellow solid by oxidation of **11b** in the presence of aqueous Oxone solution (0.18 g, 82%): mp 224−226 °C; IR (film): 1703 (C═O), 1320, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3), 2.96 (s, 3H, SO_2CH_3), 6.77 (s, 1H, pyranone H-5), 7.04−7.08 (m, 2H, phenyl H-2, H-6), 7.18−7.29 (m, 5H, phenyl H-3, H-4, H-5; 4-methylphenyl H-3, H-5), 7.32 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.71 (d, J = 8.5 Hz, 2H, 4-methylphenyl H-2, H-6), 7.73 (d, J = 8.2 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{25}H_{20}O_4S$): C, H.

6-(4-Ethylphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12c). The product was obtained as a oil by oxidation of **11c** in the presence of aqueous Oxone solution (0.21 g, 92.5%): IR (film): 1705 (C═O), 1306, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.24 (t, J = 7.6 Hz, 3H, CH_2CH_3), 2.69 (q, J = 7.6 Hz, 2H, CH_2CH_3),, 3.03 (s, 3H, SO_2CH_3), 6.85 (s, 1H, pyranone H-5), 7.11−7.15 (m, 2H, phenyl H-2, H-6), 7.26−7.38 (m, 5H, phenyl H-3, H-4, H-5; 4-ethylphenyl H-3, H-5), 7.40 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.79 (d, J = 8.5 Hz, 2H, 4-ethylphenyl H-2, H-6), 7.83 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{26}H_{22}O_4S$): C, H.

6-(4-Trifluoromethylphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12d). The product was obtained as a yellowish oil by oxidation of **11d** in the presence of aqueous Oxone solution (0.17 g, 67%): IR (film): 1735 (C═O), 1315, 1142 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 6.96 (s, 1H, pyranone H-5), 7.13−7.16 (m, 2H, phenyl

H-2, H-6), 7.24−7.39 (m, 3H, phenyl H-3, H-4, H-5), 7.41 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.75 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6), 7.81 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 8.03 (d, J = 8.2 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5). Anal. ($C_{25}H_{17}F_3O_4S$): C, H.

6-(4-Methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12e). The product was obtained as a yellow solid by oxidation of **11e** in the presence of aqueous Oxone solution (0.20 g, 86.2%): mp 218−220 °C; IR (film): 1705 (C═O), 1315, 1157 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.03 (s, 3H, SO_2CH_3), 3.89 (s, 3H, OCH_3), 6.77 (s, 1H, pyranone H-5), 6.99 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.12−7.16 (m, 2H, phenyl H-2, H-6), 7.22−7.38 (m, 3H, phenyl H-3, H-4, H-5), 7.40 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.78 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.87 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 44.5 (SO_2CH_3), 55.5 (OCH_3), 103.5 (pyranone C-5), 114.4 (4-methoxyphenyl C-3, C-5), 119.5 (pyranone C-3), 123.1 (4-methoxyphenyl C-1), 126.9 (phenyl C-3, C-5), 128.5, 128.5 and 128.7 (4-methoxyphenyl C-2, C-6; 4-methanesulfonylphenyl C-2, C-6; phenyl C-2, C-6), 129.2 (phenyl C-4), 131.9 (4-methanesulfonylphenyl C-3, C-5), 137.0 (phenyl C-1), 139.0 (4-methanesulfonylphenyl C-1), 140.1 (4-methanesulfonylphen
yl C-4), 154.7 (pyranone C-4), 159.5 (4-methoxyphenyl C-4), 161.9 (pyranone C-6), 162.1 (pyranone C-2). Anal. ($C_{25}H_{20}O_5S$): C, H.

6-(4-Ethoxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12f). The product was obtained as a yellow solid by oxidation of **11f** in the presence of aqueous Oxone solution (0.18 g, 78.5%): mp 250−252 °C; IR (film): 1698 (C═O), 1313, 1142 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.44 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 3.03 (s, 3H, SO_2CH_3), 4.08 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.77 (s, 1H, pyranone H-5), 6.97 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.11−7.14 (m, 2H, phenyl H-2, H-6), 7.25−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.39 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.78 (d, J = 8.2 Hz, 2H, 4-ethoxyphenyl H-2, H-6), 7.85 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5); ^{13}C NMR ($CDCl_3$): δ 14.7 (OCH_2CH_3), 44.5 (SO_2CH_3), 63.8 (OCH_2CH_3), 103.4 (pyranone C-5), 114.9 (4-ethoxyphenyl C-3, C-5), 119.4 (pyranone C-3), 123.2 (4-ethoxyphenyl C-1), 126.9 (phenyl C-3, C-5), 128.5, 128.5, and 128.7 (4-ethoxyphenyl C-2, C-6; 4-methanesulfonylphenyl C-2, C-6; phenyl C-2, C-6), 129.2 (phenyl C-4), 132.0 (4-methanesulfonylphenyl C-3, C-5), 137.0 (phenyl C-1), 139.0 (4-methanesulfonylphenyl C-1), 140.1 (4-methanesulfonylphenyl C-4), 154.7 (pyranone C-4), 159.6 (4-ethoxyphenyl C-4), 161.5 (pyranone C-6), 162.1 (pyranone C-2). Anal. ($C_{26}H_{22}O_5S$): C, H.

6-(4-Fluorophenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12g). The product was obtained as a yellow solid by oxidation of **11g** in the presence of aqueous Oxone solution (0.18 g, 79.6%): mp 294−296 °C; IR (film): 1709 (C═O), 1320, 1145 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 6.82 (s, 1H, pyranone H-5), 7.12−7.14 (m, 2H, phenyl H-2, H-6), 7.15 (dd, J^3_{HH} = 8.2, J^3_{FH} = 8.2 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.20−7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.40 (d, J = 8.2 Hz, 4-methanesulfonylphenyl H-2, H-6), 7.80 (d, J = 8.2 Hz, 4-methanesulfonylphenyl H-3, H-5), 7.91 (dd, J^3_{HH} = 8.2, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{24}H_{17}FO_4S$): C, H.

6-(4-Methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-(4-fluorophenyl)pyran-2-one (12h). The product was obtained as a yellow solid by oxidation of **11h** in the presence of aqueous Oxone solution (0.21 g, 88%): mp 224−226 °C; IR (film): 1709 (C═O), 1315, 1158 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 3.88 (s, 3H, OCH_3), 6.73 (s, 1H, pyranone H-5), 6.95 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 6.97 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.09 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.39 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.81 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.86 (d, J = 8.8 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{25}H_{19}FO_5S$): C, H.

6-(4-Ethoxyphenyl)-3-(4-methanesulfonylphenyl)-4-(4-fluorophenyl)pyran-2-one (12i). The product was obtained as a yellow solid by oxidation of **11i** in the presence of aqueous Oxone solution (0.19 g, 75.7%): mp 243−245 °C; IR (film): 1703 (C═O), 1310, 1152 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.45 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 2.98 (s, 3H, SO_2CH_3), 4.00 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.64 (s, 1H, pyranone H-5), 6.88 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 6.90 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.07 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.31 (d, J = 9.0 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.73 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6), 7.77 (d, J = 9.0 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{26}H_{21}FO_5S$): C, H.

6-(4-Methanesulfonylphenyl)-3,4-diphenylpyran-2-one (12j). The product was obtained as a yellow solid by oxidation of **11j** in the presence of aqueous Oxone solution (0.18 g, 82.8%): mp 178−180 °C; IR (film): 1716 (C═O), 1306, 1159 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.12 (s, 3H, SO_2CH_3), 6.97 (s, 1H, pyranone H-5), 7.16−7.39 (m, 10H, phenyl H-2, H-3, H-4, H-5, H-6), 8.07 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.10 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{24}H_{18}O_4S$): C, H.

4-(4-Methanesulfonylphenyl)-3,6-diphenylpyran-2-one (12k). The product was obtained as a yellow solid by oxidation of **11k** in the presence of aqueous Oxone solution (0.16 g, 76.3%): mp 188−190 °C; IR (film): 1723 (C═O), 1315, 1157 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 6.78 (s, 1H, pyranone H-5), 7.15−7.18 (m, 2H, phenyl H-2, H-6), 7.21−7.26 (m, 3H, phenyl H-3, H-4, H-5), 7.37 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.48−7.52 (m, 3H, phenyl H-3, H-4, H-5), 7.86 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.90−7.93 (m, 2H, phenyl H-2, H-6). Anal. ($C_{24}H_{18}O_4S$): C, H.

6-(4-Methylphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12l). The product was obtained as a oil by oxidation of **11*l*** in the presence of aqueous Oxone solution (0.17 g, 78.7%): IR (film): 1695 (C═O), 1317, 1148 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.44 (s, 3H, CH_3), 3.05 (s, 3H, SO_2CH_3), 6.74 (s, 1H, pyranone H-5), 7.12−7.17 (m, 2H, phenyl H-2, H-6), 7.18−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.34 (d, J = 8.4 Hz, 2H, 4-methylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.79 (d, J = 8.2 Hz, 2H, 4-methylphenyl H-2, H-6), 7.82 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-3, H-**5).** Anal. ($C_{25}H_{20}O_4S$): C, H.

6-(4-Ethylphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12m). The product was obtained as a yellow solid by oxidation of **11m** in the presence of aqueous Oxone solution (0.19 g, 85%): mp 173−175 °C; IR (film): 1709 (C═O), 1315, 1157 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.6 Hz, 3H, CH_2CH_3), 3.05 (s, 3H, SO_2CH_3), 2.71 (q, J = 7.6 Hz, 2H, CH_2CH_3), 6.74 (s, 1H, pyranone H-5), 7.18−7.25 (m, 5H, phenyl H-2, H-3, H-4, H-5, H-6), 7.26 (d, J = 8.5 Hz, 2H, 4-ethylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.82−7.86 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-ethylphenyl H-2, H-6). Anal. ($C_{26}H_{22}O_4S$): C, H.

6-(4-Trifluoromethylphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12n). The product was obtained as a yellow solid by oxidation of **11n** in the presence of aqueous Oxone solution (0.19 g, 75.4%): mp 203−205 °C; IR (film): 1705 (C═O), 1315, 1145 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 6.86 (s, 1H, pyranone H-5), 7.14−7.19 (m, 2H, phenyl H-2, H-6), 7.23−7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.38 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.74 (d, J = 8.5 Hz, 2H, 4-trifluoromethylphenyl H-2, H-6), 7.77 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 8.01 (d, J = 8.5 Hz, 2H, 4-trifluoromethylphenyl H-3, H-5). Anal. ($C_{25}H_{17}F_3O_4S$): C, H.

6-(4-Methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12o). The product was obtained as a yellow solid by oxidation of **11o** in the presence of aqueous

Oxone solution (0.19 g, 81.3%): mp 221−223 °C; IR (film): 1709 (C═O), 1311, 1151 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 3.89 (s, 3H, OCH_3), 6.66 (s, 1H, pyranone H-5), 6.98 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.13−7.17 (m, 2H, phenyl H-2, H-6), 7.20−7.33 (m, phenyl H-3, H-4, H-5), 7.37 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.81−7.89 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methoxyphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_5S$): C, H.

6-(4-Ethoxyphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12p). The product was obtained as a yellow solid by oxidation of **11p** in the presence of aqueous Oxone solution (0.16 g, 70%): mp 181−183 °C; IR (film): 1703 (C═O), 1315, 1157 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 3.05 (s, 3H, SO_2CH_3), 4.08 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.66 (s, 1H, pyranone H-5), 6.95 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 7.14−7.18 (m, 2H, phenyl H-2, H-6), 7.21−7.30 (m, 3H, H-3, H-4, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.83−7.87 (m, 4H, 4-ethoxyphenyl H-2, H-6; 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{26}H_{22}O_5S$): C, H.

6-(4-Fluorophenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12q). The product was obtained as a yellow solid by oxidation of **11q** in the presence of aqueous Oxone solution (0.17 g, 78%): mp 233−235 °C; IR (film): 1716 (C═O), 1312, 1143 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 6.72 (s, 1H, pyranone H-5), 7.14−7.20 (m, 4H, 4-fluorophenyl H-3, H-5; phenyl H-2, H-6), 7.21−7.25 (m, 3H, phenyl H-3, H-4, H-5), 7.26 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.84 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.87 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6). Anal. ($C_{24}H_{17}FO_4S$): C, H.

6-(4-Methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-(4-fluorophenyl)pyran-2-one (12r). The product was obtained as a yellow solid by oxidation of **11r** in the presence of aqueous Oxone solution (0.20 g, 84%): mp 228−230 °C; IR (film): 1715 (C═O), 1315, 1155 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 3.87 (s, 3H, OCH_3), 6.66 (s, 1H, pyranone H-5), 6.91−7.01 (m, 4H, 4-fluorophenyl H-3, H-5; 4-methoxyphenyl H-3, H-5), 7.11 (dd, J^3_{HH} = 8.4, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.83−7.89 (m, 4H, 4-methoxyphenyl H-2, H-6; 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{25}H_{19}FO_5S$): C, H.

6-(4-Ethoxyphenyl)-4-(4-methanesulfonylphenyl)-3-(4-fluorophenyl)pyran-2-one (12s). The product was obtained as a yellow solid by oxidation of **11s** in the presence of aqueous Oxone solution (0.23 g, 92.5%): mp 210−212 °C; IR (film): 1698 (C═O), 1316, 1157 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.44 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 3.05 (s, 3H, SO_2CH_3), 4.07 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.65 (s, 1H, pyranone H-5), 6.90−7.00 (m, 4H, fluorophenyl H-3, H-5; 4-ethoxyphenyl H-3, H-5), 7.11 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.82−7.88 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-ethoxyphenyl H-2, H-6). Anal. ($C_{26}H_{21}FO_5S$): C, H.

General Procedure for the Synthesis of 6-(4-Methylsulfanylphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12t) and 6-(4-Methylsulfanylphenyl)-3-(4-methanesulfonylphenyl)-4-(4-fluorophenyl)pyran-2-one (12u). To a stirred solution of the ethyl 4-methanesulfonylphenylacetate (**10d**, 1.55 mmol) in *tert*-butyl alcohol (10 mL) at 30 °C was added potassium *tert*-butoxide (1.90 mmol), followed by a solution of **9g** or **9k** (1.58 mmol) in *tert*-butyl alcohol (10 mL), and the reaction mixture was heated at 50−60 °C for 1−1.5 h under an argon atmosphere. The reaction mixture was cooled to 25 °C, washed with 1N HCl solution (10 mL), extracted with EtOAc (2 × 20 mL), the organic organic phase was separated, dried over Na_2SO_4, and the solvent was removed in vacuo to give a dark reddish oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (1:2, v/v or 1:3, v/v) as eluent to afford the respective title compound **12t** or **12u** (in 17 and 34% yield respectively). Some physical and spectroscopic data for **12t** and **12u** are listed below.

6-(4-Methylsulfanylphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12t). The product was obtained as a yellow solid by condensation of **9g** with **10d** in the presence of potassium *tert*-butoxide (0.24 g, 34%): mp 231−233 °C; IR (film): 1709 (C═O), 1315, 1157 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.52 (s, 3H, SCH_3), 3.03 (s, 3H, SO_2CH_3), 6.80 (s, 1H, pyranone H-5), 7.12−7.15 (m, 2H, phenyl H-2, H-6), 7.25−7.34 (m, 5H, 4-methylsulfanylphenyl H-3, H-5; phenyl H-3, H-4, H-5), 7.40 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.78−7.99 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_4S_2$): C, H.

6-(4-Methylsulfanylphenyl)-3-(4-methanesulfonylphenyl)-4-(4-fluorophenyl)pyran-2-one (12u). The product was obtained as a yellow solid by condensation of **9k** with **10d** in the presence of potassium *tert*-butoxide (0.13 g, 17.6%): mp 216−218 °C; IR (film): 1703 (C═O), 1313, 1159 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.50 (s, 3H, SCH_3), 3.04 (s, 3H, SO_2CH_3), 6.79 (s, 1H, pyranone H-5), 6.95 (dd, J^3_{HH} = 8.5, J^3_{FH} = 8.5 Hz, 2H, 4-fluorophenyl H-3, H-5), 7.10 (dd, J^3_{HH} = 8.5, J^4_{FH} = 5.2 Hz, 2H, 4-fluorophenyl H-2, H-6), 7.26 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.38 (d, J = 8.8 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.81−7.92 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{25}H_{19}FO_4S_2$): C, H.

Procedure for the Synthesis of 1-(4-Nitrophenyl)-3-phenylprop-2-yn-1-one (9s). To a mixture of phenylacetylene (1.0 g, 9.8 mmol) and copper (I) iodide (0.09 g, 0.50 mmol), Et_3N (30 mL) was added under an argon atmosphere. 4-Nitrobenzoyl chloride (12.2 mmol) was then added slowly, and the reaction mixture was stirred at 25 °C for 30 h at which time the reaction mixture was diluted with EtOAc (25 mL) and the mixture was filtered. The filtrate was evaporated under reduced pressure, and the residue obtained was further purified by a silica gel column chromatography using hexanes−ethyl acetate (1:3, v/v) as eluent to afford the title compound **9s** as a yellow solid in 24.6% yield: (0.61 g): mp 157−159 °C (lit. 162.5−163 °C[38]); IR (film): 2192 (C≡C), 1643 (C═O), 1535, 1348 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45−7.57 (m, 4H, 4-nitrophenyl H-3, H-5; phenyl H-2, H-6), 7.71 (d, J = 8.4 Hz, 2H, 4-nitrophenyl H-2, H-6), 8.27−8.39 (m, 3H, 4-phenyl H-3, H-4, H-5).

6-(4-Nitrophenyl)-3-(4-methylsulfanylphenyl)-4-phenylpyran-2-one (11t). The product was obtained as a yellow solid by condensation of **9s** with **10b** in the presence of NaH (0.24 g, 34.4%): mp 182−184 °C; IR (film): 1716 (C═O), 1532, 1351 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.46 (s, 3H, SCH_3), 6.97 (s, 1H, pyranone H-5), 7.11 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.15 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.18−7.21 (m, 2H, phenyl H-2, H-6), 7.29−7.35 (m, 3H, phenyl H-3, H-4, H-5), 8.06 (d, J = 8.8 Hz, 2H, 4-nitrophenyl H-2, H-6), 8.33 (d, J = 8.8 Hz, 2H, 4-nitrophenyl H-3, H-5). Anal. ($C_{24}H_{17}NO_4S$): C, H, N.

6-(4-Nitrophenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12v). The product was obtained as a yellow solid by the oxidation of **11t** in the presence of aqueous Oxone solution (0.18 g, 76%): mp 238−240 °C; IR (film): 1696 (C═O), 1528, 1353 (NO_2), 1320, 1148 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 7.02 (s, 1H, pyranone H-5), 7.13−7.15 (m, 2H, phenyl H-2, H-6), 7.29−7.35 (m, 3H, phenyl H-3, H-4, H-5), 7.41 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.82 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 8.08 (d, J = 8.8 Hz, 2H, 4-nitrophenyl H-2, H-6), 8.35 (d, J = 8.8 Hz, 2H, 4-nitrophenyl H-3, H-5). Anal. ($C_{24}H_{17}NO_6S$): C, H, N.

Synthesis of 6-(4-Aminophenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12w). To a stirred solution of **12v** (0.09 g, 0.22 mmol) in 95% ethanol (15 mL) was added palladium on activated carbon (4 mg). The reaction mixture was warmed to 50 °C with stirring, $NH_2NH_2 \cdot H_2O$ (0.04 mL, 0.82 mmol) was added dropwise, and the reaction mixture was refluxed at 75−78 °C for 1 h. After cooling to 25 °C, the reaction mixture was filtered, washed with water (10

mL), and extracted with EtOAc (3 × 10 mL), the organic phase was separated and dried (Na_2SO_4), and the solvent was removed in vacuo to give a yellowish brown solid which was purified by recrystallization from ethanol (0.07 g, 76%): mp 252−254 °C; IR (film): 3429 (NH_2), 1670 (C═O), 1315, 1143 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.17 (s, 3H, SO_2CH_3), 5.96 (s, 2H, NH_2), 6.63 (d, J = 8.5 Hz, 2H, 4-aminophenyl H-3, H-5), 6.92 (s, 1H, pyranone H-5), 7.19−7.21 (m, 2H, phenyl H-2, H-6), 7.22−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.36 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.68−7.76 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-aminophenyl H-2, H-6). Anal. ($C_{24}H_{19}NO_4S$): C, H, N.

Procedure for the Synthesis of 6-(4-Hydroxyphenyl)-3-(4-methanesulfonylphenyl)-4-phenylpyran-2-one (12x). A mixture of **12e** (0.27 g, 0.63 mmol) and pyridinium hydrochloride (2.5 g, 21.7 mmol) was heated at 190−210 °C for 1−1.5 h. The reaction mixture was cooled, washed with water (20 mL), and extracted with EtOAc (3 × 20 mL), and the organic phase was separated and dried (Na_2SO_4). Removal of the solvent in vacuo gave a dark brown oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (1:3, v/v or) as eluent to afford **12x** (0.05 g, 20%) as a yellowish brown solid: mp 300−301 °C; IR (film): 3462 (OH), 1705 (C═O), 1320, 1148 (SO_2) cm^{-1}; ^1H NMR (DMSO-d_6): δ 3.20 (s, 3H, SO_2CH_3), 6.77 (s, 1H, pyranone H-5), 6.88 (d, J = 8.8 Hz, 2H, 4-hydroxyphenyl H-3, H-5), 7.21−7.26 (m, 2H, phenyl H-2, H-6), 7.29−7.33 (m, 3H, phenyl H-3, H-4, H-5), 7.39 (d, J = 8.4 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.76 (d, J = 8.8 Hz, 2H, 4-hydroxyphenyl H-2, H-6), 7.86 (d, J = 8.4 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 10.24 (broad s, 1H, O*H*). Anal. ($C_{24}H_{18}O_5S$): C, H.

Preparation of 1-Ethynyl-4-methanesulfonylbenzene. To a stirred solution of 1-ethynyl-4-methylsulfanylbenzene (3.0 g, 20 mmol) in 1,4-dioxane (25 mL) at 0 °C, 50% w/v aqueous solution of Oxone (60 mmol) was added dropwise, and the reaction mixture was stirred at 25 °C for 4−5 h. The reaction mixture was diluted with water (15 mL), extracted with EtOAc (2 × 30 mL), and washed successively with brine solution and then water (15 mL each), the organic organic phase was separated and dried (Na_2SO_4), and the solvent was removed in vacuo to give a crude oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (1:2, v/v or 1:3, v/v) as eluent to afford the title compound in 74% yield as a brownish oil (2.2 g). IR (film): 2119 (C≡C), 1351, 1158 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.06 (s, 3H, SO_2CH_3), 3.30 (s, 1H, C≡C*H*), 7.66 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.90 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5).

3-(4-Methanesulfonylphenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-ol (8s). This product was obtained as a brownish oil by the reaction of 1-ethynyl-4-methanesulfonylbenzene with 4-methylthiobenzaldehyde in the presence of *n*-BuLi (2.5 g, 77.3%): IR (film): 3410 (OH), 2267 (C≡C), 1306, 1152 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.20 (d, J = 6.1 Hz, 1H,-CHO*H*), 2.50 (s, 3H, SCH_3), 3.06 (s, 3H, SO_2CH_3), 5.67 (d, J = 6.1 Hz, 1H, C*H*OH), 7.28 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.50 (d, J = 8.2 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.62 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.88 (d, J = 8.5 Hz, 2H, methanesulfonylphenyl H-3, H-5). Anal. ($C_{17}H_{16}O_3S_2$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-methylsulfanylphenyl)prop-2-yn-1-one (9t). This product was obtained as a brown oil by the oxidation of **8s** in the presence of MnO_2 (1 g, 67%): IR (film): 2200 (C≡C), 1635 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, SCH_3), 3.06 (s, 3H, SO_2CH_3), 7.31 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.84 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6), 7.92 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6). 8.09 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5). Anal. ($C_{17}H_{14}O_3S_2$): C, H.

6-(4-Methylsulfanylphenyl)-4-(4-methanesulfonylphenyl)-3-phenylpyran-2-one (12y). The product was obtained as a yellow solid by condensation of **9t** with **10a** in the presence of potassium *tert*-butoxide (0.32 g, 45.8%): mp 223−225 °C; IR (film): 1716 (C═O), 1320, 1145 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, SCH_3), 3.05 (s, 3H, SO_2CH_3), 6.73 (s, 1H, pyranone H-5), 7.13−7.17 (m, 2H, phenyl H-2, H-6), 7.20−7.25 (m, phenyl H-3, H-4, H-5), 7.26 (d, J = 8.5 Hz, 2H, 4-methylsulfanylphenyl H-3, H-5), 7.37 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.80−7.86 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methylsulfanylphenyl H-2, H-6). Anal. ($C_{25}H_{20}O_4S_2$): C, H.

1-Phenyl-3-pyridin-3-yl-prop-2-yn-1-ol (8t). The product was obtained as a dark brown semisolid by reaction of pyridin-3-ylacetylene with benzaldehyde in the presence of *n*-BuLi (0.39 g, 40%): IR (film): 3160 (OH), 2260 (C≡C), cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.89 (broad s, CHO*H*), 5.73 (s, 1H, C*H*OH), 7.24 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.7 Hz, 1H, pyridinyl H-5), 7.34−7.46 (m, 3H, phenyl H-3, H-4, H-5), 7.61−7.63 (m, 2H, phenyl H-2, H-6), 7.75 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.2 Hz, 1H, pyridinyl H-4), 8.52 (dd, $J_{5,6}$ = 4.7 Hz, $J_{4,6}$ = 2.2 Hz, 1H, pyridinyl H-6), 8.75 (d, $J_{2,4}$ = 2.2 Hz, 1H, pyridinyl H-2). Anal. ($C_{14}H_{11}NO$): C, H, N.

1-(4-Methoxyphenyl)-3-pyridin-3-yl-prop-2-yn-1-ol (8u). The product was obtained as a soild by reaction of pyridin-3-ylacetylene with 4-methoxybenzaldehyde in the presence of *n*-BuLi (1.22 g, 52.3%): mp 86−88 °C; IR (film): 3360 (OH), 2267 (C≡C), cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.83 (broad s, 1H, CHO*H*), 3.83 (s, 3H, OCH_3), 5.67 (s, 1H, C*H*OH), 6.97 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.25 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.7 Hz, H, pyridinyl H-5), 7.52 (d, J = 8.2 Hz, 2H, 4-methoxyphenyl H-2, H-6), 7.74 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-4), 8.52 (dd, $J_{5,6}$ = 4.7 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-6), 8.73 (d, $J_{2,4}$ = 2.4 Hz, 1H, pyridinyl H-2). Anal. ($C_{15}H_{13}NO_2$): C, H, N.

1-Phenyl-3-pyridin-3-yl-prop-2-yn-1-one (9u). The product was obtained as solid by oxidation of **8t** in the presence of MnO_2 (0.56 g, 60.5%): mp 66−68 °C; IR (film): 2200 (C≡C), 1635 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.35 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.7 Hz, 1H, pyridinyl H-5), 7.40−7.70 (m, 3H, phenyl H-3, H-4, H-5), 7.95 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.2 Hz, 1H, pyridinyl H-4), 8.20−8.24 (m, 2H, phenyl H-2, H-6), 8.70 (dd, $J_{5,6}$ = 4.7 Hz, $J_{4,6}$ = 2.2 Hz, 1H, pyridinyl H-6), 8.92 (d, $J_{2,4}$ = 2.2 Hz, 1H, pyridinyl H-2). Anal. ($C_{14}H_9NO$): C, H, N.

1-(4-Methoxyphenyl)-3-pyridin-3-yl-prop-2-yn-1-one (9v). The product was obtained as a white solid by oxidation of **8u** in the presence of MnO_2 (0.61 g, 57.3%): mp 126−128 °C; IR (film): 2206 (C≡C), 1642 (C═O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H, OCH_3), 6.99 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.36 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.7 Hz, 1H, pyridinyl H-5), 7.95 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-4), 8.18 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6), 8.68 (dd, $J_{5,6}$ = 4.7 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-6), 8.90 (d, $J_{2,4}$ = 2.4 Hz, 1H, pyridinyl H-2). Anal. ($C_{15}H_{11}NO_2$): C, H, N.

General Procedure for the Synthesis of 3-(4-Methanesulfonylphenyl)-6-phenyl-4-pyridin-3-yl-pyran-2-one (13a) and 6-(4-Methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-pyridin-3-yl-pyran-2-one (13b). To a stirred solution of ethyl 4-methanesulfonylphenylacetate (**10d**, 0.24 g, 1.0 mmol) in CH_2Cl_2 (10 mL) was added NaH (95% dry powder, 1.1 mmol). A solution of the 1,3-diarylprop-2-yn-1-one (**9u** or **9v**, 1 mmol) in CH_2Cl_2 (10 mL) was added slowly, and the reaction mixture was stirred at 25 °C for 1 h. Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using hexanes−ethyl acetate (1:3, v/v) as eluent to afford the respective title product **13a** or **13b** in 24−46% yield. Some physical and spectroscopic data for **13a** or **13b** are listed below.

3-(4-Methanesulfonylphenyl)-6-phenyl-4-pyridin-3-yl-pyran-2-one (13a). The product was obtained as a yellow solid by the condensation of **9u** with **10d** in the presence of NaH (0.09 g, 24%): mp 269−271 °C; IR (film): 1709 (C═O), 1327, 1162 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 6.86 (s, 1H, pyranone H-5), 7.21 (dd, $J_{4,5}$ = 7.6 Hz, $J_{5,6}$ = 4.9 Hz, 1H, pyridinyl H-5), 7.39 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-4), 7.41 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.50−7.56 (m, 3H, phenyl H-3, H-4, H-5),

7.83 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.92 (dd, $J_{5,6}$ = 4.9 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-6), 8.53 (d, $J_{2,4}$ = 2.4 Hz, 1H, pyridinyl H-2). Anal. ($C_{23}H_{17}NO_4S$): C, H, N.

6-(4-Methoxyphenyl)-3-(4-methanesulfonylphenyl)-4-pyridin-3-yl-pyran-2-one (13b). The product was obtained as a yellow solid by the condensation of **9v** with **10d** in the presence of NaH (0.2 g, 46%): mp 268−270 °C; IR (film): 1720 (C═O), 1320, 1152 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.04 (s, 3H, SO_2CH_3), 3.92 (s, 3H OCH_3), 6.74 (s, 1H, pyranone H-5), 7.00 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.19 (dd, $J_{4,5}$ = 8.0 Hz, $J_{5,6}$ = 4.9 Hz, 1H, pyridinyl H-5), 7.36 (dd, $J_{4,5}$ = 8.0 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-4), 7.40 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.81−7.90 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methoxyphenyl H-2, H-6), 8.51 (dd, $J_{5,6}$ = 4.9 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-6), 8.57 (d, $J_{2,4}$ = 2.4 Hz, 1H, pyridinyl H-2). Anal. ($C_{24}H_{19}NO_5S$): C, H, N.

Preparation of 3-(4-Methanesulfonylphenyl)-1-phenylprop-2-yn-1-one (9w) and 3-(4- Methanesulfonylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (9x). To a stirred solution of the 1,3-diarylprop-2-yn-1-one (**9l** or **9p**, 0.54 mmol) in 1,4-dioxane (10 mL) at 0 °C, a 50% w/v aqueous solution of Oxone (1.62 mmol) was added dropwise, and the reaction mixture was stirred at 25 °C for 4−5 h. The reaction mixture was diluted with water (10 mL), extracted with EtOAc (2 × 20 mL), and washed successively with brine solution and water (10 mL each), and the organic organic phase was separated and dried (Na_2SO_4). Removal of the solvent in vacuo gave a crude oil which was purified by silica gel column chromatography using hexanes−ethyl acetate (1:3, v/v) as eluent to afford the respective title compound **9w** or **9x** in 60−85% yield. Some physical and spectroscopic data for **9w** and **9x** are listed below.

3-(4-Methanesulfonylphenyl)-1-phenylprop-2-yn-1-one (9w). The product was obtained as a pale yellow solid by oxidation of **9l** in the presence of aqueous Oxone solution (0.11 g, 74%): mp 111−113 °C; IR (film): 2206 (C≡C), 1605 (C═O), 1320, 1139 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 3H, SO_2CH_3), 7.53−7.71 (m, phenyl H-3, H-4, H-5), 7.86 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.01 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 8.20−8.23 (m, 2H, phenyl H-2, H-6). Anal. ($C_{16}H_{12}O_3S$): C, H.

3-(4-Methanesulfonylphenyl)-1-(4-methoxyphenyl)prop-2-yn-1-one (9x). The product was obtained as a pale yellow solid by oxidation of **9p** in the presence of aqueous Oxone solution (0.11 g, 66.3%): mp 157−159 °C; IR (film): 2206 (C≡C), 1604 (C═O), 1320, 1140 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.10 (s, 3H, SO_2CH_3), 3.90 (s, 3H, OCH_3), 7.00 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.84 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 8.01 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 8.17 (d, J = 8.8 Hz 4-methoxyphenyl H-2, H-6). Anal. ($C_{17}H_{14}O_4S$): C, H.

Preparation of Pyridin-3-yl or Pyridin-4-yl-pyran-2-ones (13c−f). To a stirred solution of either the pyridin-3-yl or pyridin-4-ylacetic acid ester (1.0 mmol) in CH_2Cl_2 (10 mL) was added NaH (95% dry powder, 1.1 mmol). A solution of the respective 1,3-diarylprop-2-yn-1-one (**9w−x,** 1.0 mmol) in CH_2Cl_2 (10 mL) was added slowly, and the reaction mixture was allowed to stir at 25 °C for 1 h. Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using hexanes−ethyl acetate (1:3, v/v) as eluent to afford the respective title product **13c−f** in 24−46% yield. Some physical and spectroscopic data for **13c−f** are listed below.

4-(4-Methanesulfonylphenyl)-6-phenyl-3-pyridin-3-yl-pyran-2-one (13c). The product was obtained as yellow solid by the condensation of **9w** with the pyridin-3-ylacetic acid ester in the presence of NaH (0.15 g, 38.2%): mp 235−237 °C; IR (film): 1690 (C═O), 1313, 1152 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 3H, SO_2CH_3), 6.82 (s, 1H, pyranone H-5), 7.24 (dd, $J_{4,5}$ = 7.0 Hz, $J_{5,6}$ = 4.9 Hz, 1H, pyridinyl H-5), 7.29 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.41−7.50 (m, 3H, phenyl H-3, H-4, H-5), 7.71 (dd, $J_{4,5}$ = 7.0 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-4), 7.88 (d, J = 8.5 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.92−7.94 (m, 2H, phenyl H-2, H-6), 8.28 (dd, $J_{5,6}$ = 4.9 Hz, $J_{4,6}$ = 2.4 Hz, 1H, pyridinyl H-6), 8.48 (d, $J_{2,4}$ = 2.4 Hz, 1H, pyridinyl H-2). Anal. ($C_{23}H_{17}NO_4S$): C, H, N.

6-(4-Methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-pyridin-3-yl-pyran-2-one (13d). The product was obtained as a yellow solid by the condensation of **9x** with the pyridin-3-ylacetic acid ester in the presence of NaH (0.18 g, 42.3%): mp 242−244 °C; IR (film): 1703 (C═O), 1306, 1165 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.05 (s, 3H, SO_2CH_3), 3.89 (s, 3H OCH_3), 6.70 (s, 1H, pyranone H-5), 7.00 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.25 (dd, $J_{4,5}$ = 7.9 Hz, $J_{5,6}$ = 5.2 Hz, 1H, pyridinyl H-5), 7.38 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.75 (dd, $J_{4,5}$ = 7.9 Hz, $J_{4,6}$ = 1.8 Hz, 1H, pyridinyl H-4), 7.86−7.91 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methoxyphenyl H-2, H-6), 8.27 (dd, $J_{5,6}$ = 5.2 Hz, $J_{4,6}$ = 1.8 Hz, 1H, pyridinyl H-6), 8.49 (d, $J_{2,4}$ = 1.8 Hz, 1H, pyridinyl H-2). Anal. ($C_{24}H_{19}NO_5S$): C, H, N.

4-(4-Methanesulfonylphenyl)-6-phenyl-3-pyridin-4-yl-pyran-2-one (13e). The product was obtained as a yellow solid by the condensation of **9x** with the pyridin-4-ylacetic acid ester in the presence of NaH (0.09 g, 22.4%): mp 255−257 °C; IR (film): 1712 (C═O), 1320, 1152 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.07 (s, 3H, SO_2CH_3), 6.80 (s, 1H, pyranone H-5), 7.11 (d, $J_{2,3}$ = $J_{5,6}$ = 5.5 Hz, 2H, pyridinyl H-3, H-5), 7.39 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.44−7.53 (m, 3H, phenyl H-3, H-4, H-5), 7.89 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-3, H-5), 7.92−7.95 (m, 2H, phenyl H-2, H-6), 8.50 (d, $J_{2,3}$ = $J_{5,6}$ = 5.5 Hz, 2H, pyridinyl H-2, H-6). Anal. ($C_{23}H_{17}NO_4S$): C, H, N.

6-(4-Methoxyphenyl)-4-(4-methanesulfonylphenyl)-3-pyridin-4-yl-pyran-2-one (13f). The product was obtained as a yellow solid by the condensation of **9x** with the pyridin-4-ylacetic acid ester in the presence of NaH (0.17 g, 41.3%): mp 240−242 °C; IR (film): 1716 (C═O), 1320, 1145 (SO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.06 (s, 3H, SO_2CH_3), 3.90 (s, 3H OCH_3), 6.69 (s, 1H, pyranone H-5), 6.98 (d, J = 8.5 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.13 (d, $J_{2,3}$ = $J_{5,6}$ = 5.5 Hz, 2H, pyridinyl H-3, H-5), 7.38 (d, J = 8.2 Hz, 2H, 4-methanesulfonylphenyl H-2, H-6), 7.85−7.93 (m, 4H, 4-methanesulfonylphenyl H-3, H-5; 4-methoxyphenyl H-2, H-6), 8.49 (d, $J_{2,3}$ = $J_{5,6}$ = 5.5 Hz, 2H, pyridinyl H-2, H-6). Anal. ($C_{24}H_{19}NO_5S$): C, H, N.

Preparation of 4-Azidophenylacetic acid (15). To an ice cold solution of 4-aminophenylacetic acid (**14**, 2.0 g, 13.2 mmol) in concentrated HCl (20 mL) was added an aqueous solution of $NaNO_2$ (13.3 mmol, 0.92 g in 70 mL water) slowly with stirring. After 15 min, an aqueous solution of NaN_3 (132 mmol, 8.6 g in 200 mL of water) was added at 0 °C over a period of 15 min after which the reaction mixture was stirred at 25 °C for 15−20 min. The reaction mixture was extracted with EtOAc (3 × 20 mL), the organic phase was separated and dried over Na_2SO_4, and the solvent was removed in vacuo to give brown crystals of **15** (2.2 g, 94%): mp 86−88 °C; IR (film): 2119 (N_3), 1710 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 2H, CH_2CO), 6.98 (d, J = 8.8 Hz, 2H, 4-azidophenyl H-3, H-5), 7.29 (d, J = 8.8 Hz, 2H, 4-azidophenyl H-2, H-6). Anal. ($C_8H_7N_3O_2$): C, H, N.

Preparation of Ethyl 4-Azidophenylacetate (16). To a stirred solution of 4-azidophenylacetic acid (**15**, 1.0 g, 5.6 mmol) in concentrated H_2SO_4 (1.1 mL) was added ethanol (5.2 mL of 95%), and the reaction mixture was refluxed at 70−75 °C for 3−4 h. The reaction mixture was diluted with EtOAc (15 mL), $NaHCO_3$ (1 g) was added and filtered, and the organic fraction was dried (Na_2SO_4). The EtOAc fraction was evaporated to give a brownish oil (1 g, 87%): IR (film): 2131 (N_3), 1739 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.0 Hz, 3H, $COCH_2CH_3$), 3.59 (s, 2H, CH_2CO), 4.12 (q, J = 7.0 Hz, 2H, $COCH_2CH_3$), 6.98 (d, J = 8.8 Hz, 2H, 4-azidophenyl H-3, H-5), 7.24 (d, J = 8.8 Hz, 2H, 4-azidophenyl H-2, H-6). Anal. ($C_{10}H_{11}N_3O_2$): C, H, N.

General Procedure for the Synthesis of 6-(4-Methoxy, ethoxy, or 4-methylsulfanylphenyl)-3-(4-azidophenyl)-4-phenylpyran-2-ones (17a−c). To a stirred solution of **16** (0.22 g, 1.7 mmol) in CH_2Cl_2 (10 mL) was added NaH (95%

dry powder, 1.9 mmol). The 1,3-diarylprop-2-yn-1-one (**9e**−**g**, 1.7 mmol) in CH_2Cl_2 (10 mL) was added slowly, and the reaction mixture was allowed to stir at 25 °C for 1 h. Removal of the solvent in vacuo gave a residue that was purified by silica gel column chromatography using hexanes−ethyl acetate (3:1, v/v) as eluent to afford the respective product **17a**−**c** in 28−33% yield. Some physical and spectroscopic data for **17a**−**c** are listed below.

6-(4-Methoxyphenyl)-3-(4-azidophenyl)-4-phenylpyran-2-one (17a). The product was obtained as orange crystals by the condensation of **9e** with **16** in the presence of NaH (0.20 g, 30.7%): mp 184−186 °C; IR (film): 2112, 2105 (N_3), 1716 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.89 (s, 3H, OCH_3), 6.73 (s, 1H, pyranone H-5), 6.88 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 6.97 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-3, H-5), 7.17−7.21 (m, 4H, 4-azidophenyl H-2, H-6; phenyl H-2, H-6), 7.26−7.31 (m, 3H, phenyl H-3, H-4, H-5), 7.85 (d, J = 8.8 Hz, 2H, 4-methoxyphenyl H-2, H-6); ^{13}C NMR ($CDCl_3$): δ 55.5 (OCH_3), 103.5 (pyranone C-5), 114.4 (4-methoxyphenyl C-3, C-5), 118.6 (4-azidophenyl H-3, H-5), 120.8 (pyranone C-3), 123.8 (4-methoxyphenyl C-1), 127.3 (phenyl C-3, C-5), 128.5, 128.6 and 128.7 (phenyl C-4, 4-methoxyphenyl C-2, C-6; 4-azidophenyl C-2, C-6), 130.7 (4-azidophenyl C-4), 132.4 (4-phenyl C-2, C-6), 137.9 (phenyl C-1), 139.1 (4-azidophenyl C-1), 153.2 (pyranone C-4), 158.5 (4-methoxyphenyl C-4), 161.7 (pyranone C-6), 162.6 (pyranone C-2). Anal. ($C_{24}H_{17}N_3O_3$): C, H, N.

6-(4-Ethoxyphenyl)-3-(4-azidophenyl)-4-phenylpyran-2-one (17b). The product was obtained as a orange solid by the condensation of **9f** with **16** in the presence of NaH (0.24 g, 35.6%): mp 169−171 °C; IR (film): 2119, 2109 (N_3), 1709 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 3.98 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.64 (s, 1H, pyranone H-5), 6.75 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-3, H-5), 6.88 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.06−7.12 (m, 4H, 4-azidophenyl H-2, H-6; phenyl H-2, H-6), 7.14−7.24 (m, 3H, phenyl H-3, H-4, H-5), 7.74 (d, J = 8.8 Hz, 2H, 4-ethoxyphenyl H-2, H-6); ^{13}C NMR ($CDCl_3$): δ 14.7 (OCH_2CH_3), 63.7 (OCH_2CH_3), 103.4 (pyranone C-5), 114.8 (4-ethoxyphenyl C-3, C-5), 118.6 (4-azidophenyl H-3, H-5), 120.7 (pyranone C-3), 123.6 (4-ethoxyphenyl C-1), 127.3 (phenyl C-3, C-5), 128.4, 128.6 and 128.7 (phenyl C-4, 4-ethoxyphenyl C-2, C-6; 4-azidophenyl C-2, C-6), 130.7 (4-azidophenyl C-4), 132.4 (4-phenyl C-2, C-6), 137.9 (phenyl C-1), 139.1 (4-azidophenyl C-1), 153.2 (pyranone C-4), 158.6 (4-ethoxyphenyl C-4), 161.2 (pyranone C-6), 162.7 (pyranone C-2). Anal. ($C_{25}H_{19}N_3O_3$): C, H, N.

6-(4-Methylsulfanylphenyl)-3-(4-azidophenyl)-4-phenylpyran-2-one (17c). The product was obtained as a pale yellow solid by the condensation of **9g** with **16** in the presence of NaH (0.23 g, 33.6%): mp 170−172 °C; IR (film): 2112, 2106 (N_3), 1709 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.55 (s, 3H, SCH_3), 6.79 (s, 1H, pyranone H-5), 6.88 (d, J = 8.5 Hz, 2H, 4-azidophenyl H-3, H-5), 7.15−7.20 (m, 4H, 4-azidophenyl H-2, H-6; phenyl H-2, H-6), 7.21−7.32 (m, 5H, 4-methylsulfanylphenyl H-3, H-5; phenyl H-3, H-4, H-5), 7.80 (d, J = 8.8 Hz, 2H, 4-methylsulfanylphenyl H-2, H-6); ^{13}C NMR ($CDCl_3$): δ 15.1 (SCH_3), 104.2 (pyranone C-5), 118.6 (4-azidophenyl C-3, C-5), 121.6 (pyranone C-3), 125.8 (4-methylsulfanylphenyl C-3, C-5), 127.5 (4-methylsulfanylphenyl C-1), 127.3 (phenyl C-3, C-5), 128.5, 128.5 and 128.8 (phenyl C-4, 4-methylsulfanylphenyl C-2, C-6; 4-azidophenyl C-2, C-6), 130.5 (4-azidophenyl C-4), 132.4 (4-phenyl C-2, C-6), 137.7 (phenyl C-1), 139.2 (4-azidophenyl C-1), 142.9 (4-methylsulfanylphenyl C-4), 152.9 (pyranone C-4), 158.1 (pyranone C-6), 162.5 (pyranone C-2). Anal. ($C_{24}H_{17}N_3O_2S$): C, H, N.

Cyclooxygenase Inhibition Studies. The ability of the test compounds **12**, **13**, and **17** 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) was added 10 μL of various concentrations of test drug solutions (0.001, 0.1, 1, 10, 50, 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 was 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).

Antiinflammatory Assay. The test compounds were evaluated using the in vivo rat carrageenan-induced foot paw edema model reported previously.[39,40]

Analgesic Assay. Analgesic activity was determined using the 4% sodium chloride-induced writhing (abdominal constriction) assay as described previously.[41]

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-2 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. 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) or extensible systematic force field (ESFF) 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 200-step equilibration for over 5000 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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