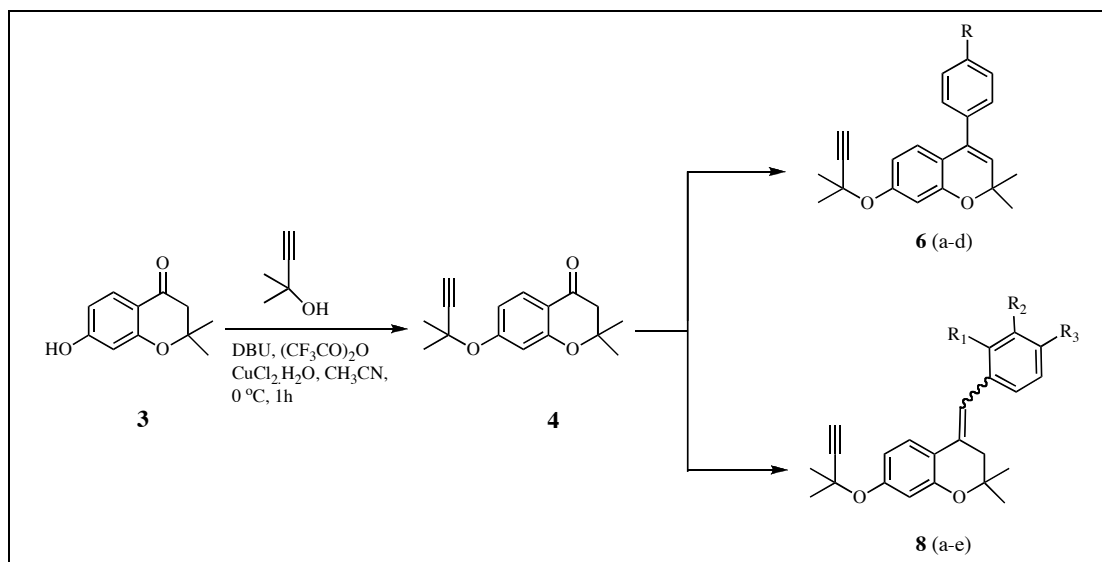


Babak H. Alizadeh^a, Alireza Foroumadi^b, Abass Shafiee^{*b}^a Iranian Research Institute of Plant Protection, Shahid Chamran Avenue, Yaman St. No.1;
PO.Box:1454,Tehran^b Department of Chemistry, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran
University of Medical Sciences, Tehran,14174 Iran. ashafiee@ams.ac.ir

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Trifluoromethansulfonic acid (TFA) was found a proper reagent for regioselectively ring closure of resorcinol to afford 7-hydroxy-2,2-dimethyl-2,3-dihydrochromen-4-one **3**. The propargylation of **3** gave rise to 2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-2,3-dihydrochromen-4-one **4**. Condensation of **4** with substituted phenyl or benzyl Grignard reagents afforded substituted phenyl or benzylidene chromenes **6a-d** and 4-(substitutedbenzylidene)-3,4-dihydro chromenes **8a-e**, respectively.

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INTRODUCTION

2,2-Dimethyl-3-chromene ring as a common scaffold in several novel synthetic and natural compounds has shown considerable biological activities. Several compounds with the 2,2-dimethyl-3-chromene moiety were tested and their results showed that chromenes with an aromatic ring substituted at the C-4 position may act as potent retinoic acid receptor α -selective antagonists [1,2]. Moreover, the chromene derivatives themselves have several biological activities, and excellent results have been shown in a decade of extensive research [3,4]. In addition, benzopyranes are commonly found in many natural products, in particular, the flavonoids and the glyasperins (Figure 1). Furthermore, a recent study has shown that the propargyl moiety present in chromone derivatives is essential for biological activity [5,6,7]. The latter hypothesis prompted us to investigate the possible utilization of dimethylpropargyl moiety for the preparation of 4-(substituted phenyl) chromenes **6a-d** and 4-(substitutedbenzylidene)-3,4-dihydro chromenes **8a-e** as

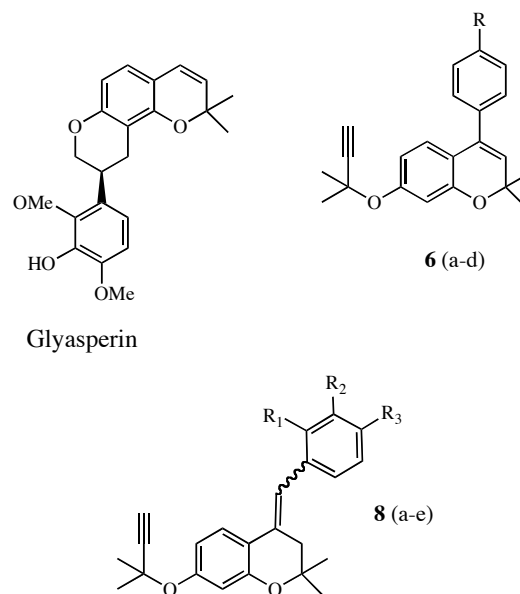


Figure 1

possible biologically active compounds. Herein we report the synthesis of (**6a-d**) and (**8a-e**).

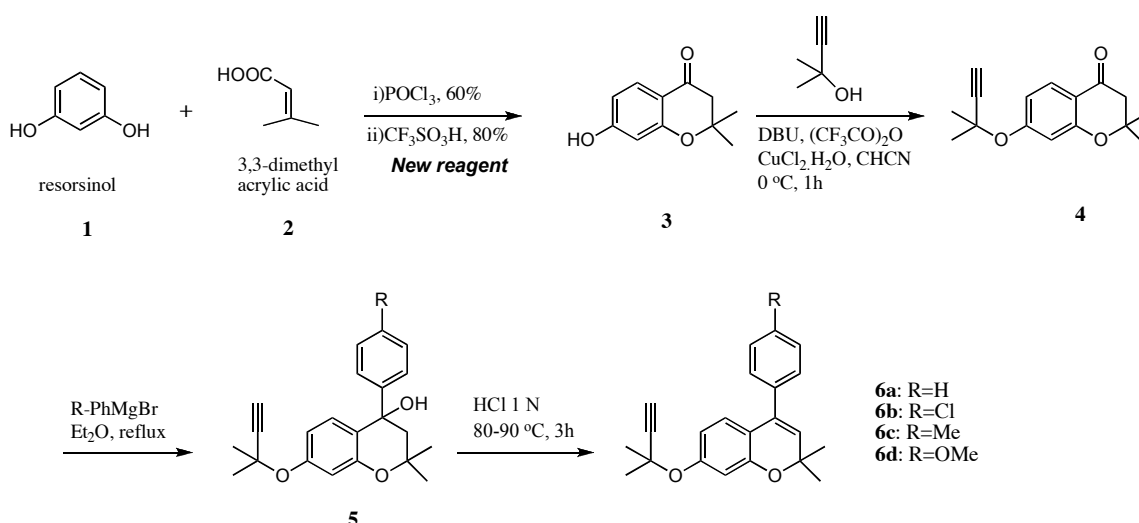
RESULTS AND DISCUSSION

According to retrosynthetic analysis, the known compound **3** is the key intermediate for the synthesis of **6a-d** and **8a-e**. A survey in the literature showed that most procedures for the synthesis of compound **3** required severe reaction conditions, lack of generality and they were low yielding [3,8]. One important entry into this structural type is through the treatment of resorcinol with 3,3-dimethylacrylic acid in the presence of a Lewis acid

yield of the propargylation of **3** depended on the reaction temperature. Thus, the temperature of a solution of compound **3** in acetonitrile was maintained at -5°C for 45 minutes followed by carefully addition of resultant triflate into the reaction mixture. Treatment of various substituted phenyl Grignard reagents with **4**, using the normal reaction condition, afforded the required alcohol (**5**), which after elimination of water afforded the corresponding olefin (**6a-d**), in good yield.

For the preparation of compound **8**, the Wittig reaction, namely, reaction of substituted benzyl triphenylphosphonium with **4** was tried. However, compounds **8** could

Scheme 1



such as POCl_3 or CF_3COOH [9,10]. As Shown in Scheme 1, the key intermediate **3** was synthesized through the reaction of resorcinol with 3,3-dimethylacrylic acid, POCl_3 and ZnCl_2 and under the best condition gave 60% yield of compound **3**. Furthermore, the work up was difficult, too sluggish, and basically, changing the condition of the reaction had no appreciable effect on increasing the yield. Observing this unsatisfactory result, we turned our attention to develop an efficient, general, and practical method. We observed that the reaction of compound **2** with 3 equivalent of Lewis acid $\text{CF}_3\text{SO}_3\text{H}$ at 70°C gave smoothly compound **3** in good 80% overall yield (Scheme 1).

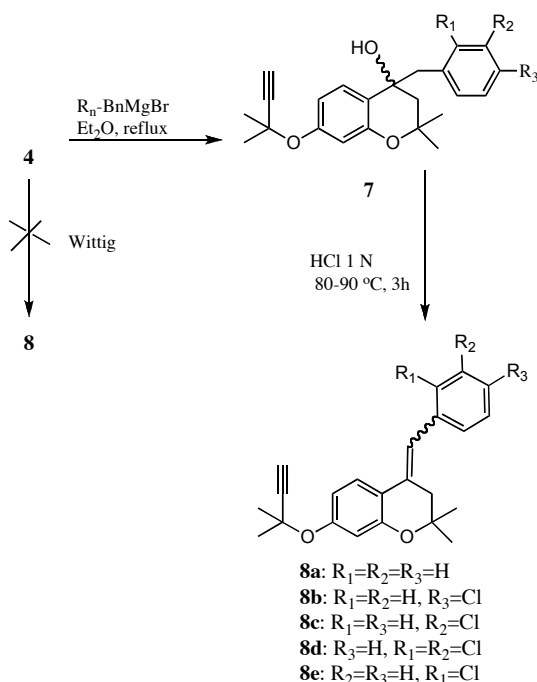
In the next step, introduction of dimethyl propargyl into **3** was investigated. The latter group was shown to be essential for biological activity [4,5,6]. Treatment of 2-methylbut-3-yn-2-ol with trifluoroacetic anhydride gave intermediate triflate which has been used as an effective alkylating reagent in the presence of DBU and $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ in acetonitrile [11]. Different experimental conditions were conducted and results showed that the

not be isolated [12]. Finally the reaction of substituted benzyl magnesium bromide with compound **4** in ether under reflux afforded an unstable tertiary alcohols **7** which was converted to **8a-8e** using a hot acidic condition (Scheme 2) [13, 14]. Compounds **8a-8e** was obtained as 90:10 to 60:40 mixtures of *E* and *Z*-isomers. The structures of compounds were established by NMR. In *E*-isomers H_5 of *E*-chromen-4-one was more deshielded than the *Z*-isomer. In fact in the *Z*-isomer the phenyl ring has shielded the H_5 of chromene-4-one.

CONCLUSION

In conclusion, we have described an efficient, general, and practical method for the preparation of **3** under mild conditions, using trifluoromethanesulfonic acid (TFA) as a proper Lewis acid. Two types of the new 4-substituted derivatives of **6a-d** and **8a-e** were prepared via the reaction of several substituted phenyl and benzyl magnesium halides with **4** as a versatile precursor for the preparation of various derivatives of chromenes.

Scheme 2



EXPERIMENTAL

General: 1H nmr spectra were measured using a Bruker 500 spectrometer and chemical shifts are expressed as δ (ppm) with tetramethylsilane as internal standard. The ir spectra were obtained on a Shimadzu 470 spectrophotometer (potassium bromide disks). The purity of the compounds was monitored by thin layer chromatography. Elemental analyses were carried out on CHN rapid elemental analyzer (GmbH-Germany) for C and H, and the results are within $\pm 0.4\%$ of the theoretical values. All substrates and reagents were obtained from Merck and Aldrich Chemical Co.

7-Hydroxy-2,2-dimethyl-2,3-dihydrochromen-4-one (3). To a stirred mixture of resorcinol (2.0 g, 18.2 mmol) and 3,3-dimethylacrylic acid (1.8 g, 18.2 mmol) was added trifluoromethanesulfonic acid (5.5 mL, 54.6 mmol) in one portion. The solution was warmed to 70 °C for 2 hours, cooled to room temperature over 15 min, and poured into chloroform (40 mL). The solution was slowly poured into water (50 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and filtered. Concentration in vacuum gave 2.7 g (14.6 mmol, 80% yield) of an orange solid [9]. mp 164-165 °C; 1H nmr (deuteriochloroform): δ 1.43 (s, 6H, 2- CH_3), 2.61 (s, 2H, $-CH_2-C=O$), 6.29 (d, 1H, $J = 2.1$ Hz, H-8), 6.45 (dd, 1H, $J = 2.1, 8.5$ Hz, H-6), 7.61 (d, 1H, $J = 8.5$ Hz, H-5); ir (Nujol): 3200 (OH), 1655 (C=O) cm^{-1} ; ms: m/z (%) 193 (39), 178 (100), 132 (11), 102 (39), 78 (24). Anal. Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.98; H, 6.13.

2,2-Dimethyl-7-(2-methylbut-3-yn-2-yloxy)-2,3-dihydrochromen-4-one (4). To a solution of 2-methyl-3-butyn-2-ol (2 mL, 20.83 mmol) in anhydrous acetonitrile (10 mL) under argon and cooled in an ice-salt bath at -5 °C, was added DBU (4.7 mL, 31.25 mmol) dropwise. Trifluoroacetic anhydride

(2.9 mL, 20.83 mmol) was added over a 30 minutes period while keeping the temperature at less than 0 °C. The solution was allowed to stir at 0 °C for 1 hour before addition to 3.

To a solution of 3 (1 g, 5.2 mmol) in CH_3CN (10 mL) under argon and cooled in an ice-salt bath (-5 °C) was added DBU (1.1 mL, 7.8 mmol) and $CuCl_2 \cdot 2H_2O$ (44 mg, 0.44 mmol) and stirred for 30 minutes.

This solution, maintained at -5 °C, was added to the 2-methyl-3-butyn-2-ol solution over a 50 minutes period while keeping the temperature below 0 °C. After stirring for 30 minutes at 0 °C, water was added and the mixture was concentrated at reduced pressure and residue was extracted by $EtOAc$ (3 x 50 mL). The combined organic phase was washed with 1N HCl (3 x 50 mL), saturated $NaHCO_3$, and brine. After drying with Na_2SO_4 , the solvent was removed at reduced pressure to give a residue, which was purified by column chromatography (silicagel, 30g) and eluted by hexane/ethyl acetate (4:1) to provide the compound 4 (1.09 g, 4.2 mmol, 81%) as pale yellow oil and also starting compound 3 (0.1 g, 0.5 mmol, 10%). 1H nmr (deuteriochloroform): δ 1.48 (s, 3H, 2- CH_3), 1.49 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.74 (s, 3H, CH_3), 2.70 (s, 3H, $-CH_2-C=O$, $CH \equiv C$), 6.79 (dd, 1H, $J = 2.3, 8.7$ Hz, H-6), 6.8 (d, 1H, $J = 2.1$ Hz, H-8), 7.76 (d, 1H, $J = 8.7$ Hz, H-5); ir (Nujol): 3290 ($\equiv C-H$), 2132 ($C \equiv C$), 1655 (C=O) cm^{-1} ; ms: m/z (%) 258 (M^+ , 19), 192 (33), 177 (100), 137 (54), 107 (32), 67 (53). Anal. Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.12; H, 6.93.

2,2-Dimethyl-7-(2-methylbut-3-yn-2-yloxy)-4-phenyl-2H-chromene (6a). To a stirred solution of 4 (0.1 g, 0.4 mmol), in dry ether (3 mL) was added phenylmagnesium bromide (1.25 mL, 1 mmol) under argon. The resulting mixture was stirred and reflux for 18 hours. After cooling, the organic phase was washed with 1 N HCl (3 x 5 mL). The solvent was evaporated under reduce pressure to give an oil. To this oily residue was added 2 N HCl (5 mL) and refluxed for 12 hours, after cooling, it was extracted with ethyl acetate (3 x 10 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ and dried with anhydrous Na_2SO_4 . After concentration, the residue was purified by flash column chromatography (silica gel = 10 g, hexane / $EtOAc = 5$) to give 6a (1.25 g, 4.99 mmol, 90 %) as colorless oil. 1H nmr (deuteriochloroform): δ 1.54 (s, 6H, CH_3), 1.69 (s, 6H, CH_3), 2.62 (s, 1H, $CH \equiv C$), 5.55 (s, 1H, H-3), 6.71-6.73 (dd, 1H, $J = 2.47, 8.46$ Hz, H-6), 6.85 (d, 1H, $J = 2.38$ Hz, H-8), 6.93 (d, 1H, $J = 8.46$ Hz, H-5), 7.38-7.42 (m, 5H, aromatic); ir (Nujol): 3290 ($\equiv C-H$), 2158 ($C \equiv C$), 1608 (C=C) cm^{-1} ; ms: m/z (%) 318 (M^+ , 23), 251 (10), 237 (100), 208 (20), 165 (21), 119 (15), 91 (20). Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.68; H, 6.91.

4-(4-Chlorophenyl)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-2H-chromene (6b). A colorless oil (85%), 1H nmr (deuteriochloroform): δ 1.51 (s, 6H, CH_3), 1.71 (s, 6H, CH_3), 2.63 (s, 1H, $CH \equiv C$), 5.54 (s, 1H, H-3), 6.72-6.74 (dd, 1H, $J = 2.47, 8.43$ Hz, H-6), 6.85 (d, 1H, $J = 2.41$ Hz, H-8), 6.89 (d, 1H, $J = 8.46$ Hz, H-5), 7.32 (d, 2H, $J = 8.41$ Hz, aromatic), 7.39-7.40 (d, 2H, $J = 8.41$ Hz, CH of CH_2); ir (Nujol): 3296 ($\equiv C-H$), 2158 ($C \equiv C$), 1604 (C=C) cm^{-1} ; ms: m/z (%) 353 (M^+ , 24), 352 (71), 337 (60), 286 (38), 284 (51), 271 (100), 242 (37), 222 (43), 188 (60), 152 (87), 133 (39), 91 (42). Anal. Calcd. for $C_{22}H_{21}ClO_2$: C, 74.89; H, 6.00. Found: C, 74.91; H, 5.73.

2,2-Dimethyl-7-(2-methylbut-3-yn-2-yloxy)-4-p-tolyl-2H-chromene (6c). A colorless oil (65%), 1H nmr (deuteriochloroform): δ 1.51 (s, 6H, CH_3), 1.70 (s, 6H, CH_3), 2.43 (s, 3H, $Ph-CH_3$), 2.62 (s, 1H, $CH \equiv C$), 5.53 (s, 1H, H-3), 6.70-6.72

(dd, 1H, $J = 2.42$, $J = 8.45$ Hz, H-6), 6.85 (d, 1H, $J = 2.41$ Hz, H-8), 6.94-6.96 (d, 1H, $J = 8.57$ Hz, H-5), 7.23 (d, 2H, $J = 7.9$ Hz, aromatic), 7.28-7.29 (d, 2H, $J = 7.9$ Hz, aromatic); ir (Nujol): 3283 ($\equiv\text{C-H}$), 2105 ($\text{C}\equiv\text{C}$), 1622 ($\text{C}=\text{C}$) cm^{-1} ; ms: m/z (%) 332 (M^+ , 25), 258 (23), 250 (100), 243 (25), 176 (99), 137 (26), 91 (23), 83 (32). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_2$: C, 83.10; H, 7.28. Found: C, 83.03; H, 7.44.

4-(4-Methoxyphenyl)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-2H-chromene (6d). A colorless oil (70%), ^1H nmr (deuteriochloroform): δ 1.52 (s, 6H, CH_3), 1.70 (s, 6H, CH_3), 2.62 (s, 1H, $\text{CH}\equiv\text{C}$), 3.89 (s, 3H, $-\text{OCH}_3$), 5.51 (s, 1H, H-3), 6.72 (dd, 1H, $J = 2.4$, 8.50 Hz, H-6), 6.83 (d, 1H, $J = 6.5$ Hz, Ph), 6.85 (d, 1H, $J = 2.4$ Hz, H-8), 6.95 (d, 1H, $J = 8.41$ Hz, H-5), 6.97 (d, 1H, $J = 8.5$ Hz, Ph), 7.33 (d, 1H, $J = 6.5$ Hz, Ph), 7.43 (d, 1H, $J = 8.5$ Hz, Ph); ir (Nujol): 3288 ($\equiv\text{C-H}$), 2117 ($\text{C}\equiv\text{C}$), 1611 ($\text{C}=\text{C}$) cm^{-1} ; ms: m/z (%) 348 (M^+ , 22), 333 (34), 265 (100), 233 (22), 214 (76), 151 (62), 148 (72), 135 (44), 90 (72). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_3$: C, 79.28; H, 6.94. Found: C, 78.98; H, 6.72.

4-Benzylidene-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-3,4-dihydro-2H-chromene (8a). A colorless oil (85%), as *E* and *Z* mixture (90:10): ^1H nmr (deuteriochloroform): δ 1.30 and 1.32 (2s, 3H, $2-\text{CH}_3$), 1.44 and 1.45 (2s, 3H, $2-\text{CH}_3$), 1.66 and 1.67 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.70 and 1.71 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.78 and 1.80 (2d, 2H, $J = 2.8$ Hz, $3-\text{CH}_2$), 2.75 (bs, 1H, $\text{CH}\equiv\text{C}$), 6.69 and 6.71 (2d, 1H, $J = 2.4$ Hz, H_8), 6.75 and 6.79 (2dd, 1H, $J = 2.4$ Hz, 8.4 Hz, H_6), 7.10 (bs, 1H, $\text{Ph-CH}=\text{C}$), 7.22 - 7.36 (m, 5H, Ph), 7.39 and 7.59 (2d, 1H, $J = 8.4$ Hz, H_5); ir (Nujol): 3290 ($\equiv\text{C-H}$), 2128 ($\text{C}\equiv\text{C}$), 1606 ($\text{C}=\text{C}$) cm^{-1} ; ms: m/z (%) 322 (M^+ , 91), 280 (13), 242 (12), 202 (22), 188 (100), 150 (94), 84 (24). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{24}\text{O}_2$: C, 83.10; H, 7.28. Found: C, 83.31; H, 7.01.

4-(4-Chlorobenzylidene)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-3,4-dihydro-2H-chromene (8b). A colorless oil (90%) as *E* and *Z* mixture (67:33): ^1H nmr (deuteriochloroform): δ 1.31 and 1.32 (2s, 3H, $2-\text{CH}_3$), 1.44 and 1.45 (2s, 3H, $2-\text{CH}_3$), 1.65 and 1.67 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.69 and 1.71 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.77 and 1.79 (2d, 2H, $J = 2.8$ Hz, $3-\text{CH}_2$), 2.70 and 2.71 (2s, 1H, $\text{CH}\equiv\text{C}$), 6.68 and 6.75 (2d, 1H, $J = 2.4$ Hz, H_8), 6.76 and 6.78 (2dd, 1H, $J = 2.4$ Hz, 8.4 Hz, H_6), 7.04 (bs, 1H, $4-\text{ClPh-CH}=\text{C}$), 7.21 and 7.26 (2d, 2H, $J = 8.4$ Hz, $\text{H}_{3,5}-4-\text{ClPh}$), 7.31 and 7.37 (2d, 2H, $J = 8.4$ Hz, $\text{H}_{2,6}-4-\text{ClPh}$), 7.36 and 7.54 (2d, 1H, $J = 8.4$ Hz, H_5). IR (film) cm^{-1} : 3288 ($\equiv\text{C-H}$), 2130 ($\text{C}\equiv\text{C}$), MS m/z (%): 368 ($\text{M}^+ + 2$, 32), 366 (M^+ , 100), 351 (59), 302 (48), 284 (98), 250 (26), 189 (20), 175 (57), 124 (99), 89 (78), 67 (87). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{23}\text{ClO}_2$: C, 75.30; H, 6.32. Found: C, 75.53; H, 6.45.

4-(3-Chlorobenzylidene)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-3,4-dihydro-2H-chromene (8c). A colorless oil (85%) as *E* and *Z* mixture (60:40): ^1H nmr (deuteriochloroform): δ 1.32 and 1.33 (2s, 3H, $2-\text{CH}_3$), 1.45 and 1.46 (2s, 3H, $2-\text{CH}_3$), 1.66 and 1.67 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.70 and 1.71 (2s, 3H, $\text{C}\equiv\text{CCH}_3$), 1.78 and 1.79 (2d, 2H, $J = 2.9$ Hz, $3-\text{CH}_2$), 2.72 and 2.73 (2s, 1H, $-\text{C}\equiv\text{CH}$), 6.69 and 6.77 (2d, 1H, $J = 2.4$ Hz, H_8), 6.77 and 6.82 (2dd, 1H, $J = 2.4$ Hz, 8.4 Hz, H_6), 7.07 (bs, 1H, $3-\text{ClPh-CH}=\text{C}$), 7.15 and 7.30 (m, 4H, $3-\text{ClPh}$), 7.35 and 7.51 (2d, 1H, $J = 8.4$ Hz, H_5). IR (film) cm^{-1} : 3290 ($\equiv\text{C-H}$), 2128 ($\text{C}\equiv\text{C}$), MS: m/z (%): 368 ($\text{M}^+ + 2$, 12), 364 (M^+ , 37), 350 (14), 301 (37), 298 (73), 283 (100), 132 (14), 124 (22), 90 (13), 66 (24). *Anal.* Calcd. for $\text{C}_{22}\text{H}_{23}\text{ClO}_2$: C, 75.30; H, 6.32. Found: C, 75.55; H, 6.14.

4-(2,3-Dichlorobenzylidene)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-3,4-dihydro-2H-chromene (8d). A colorless oil (80%) as *E* and *Z* mixture (95:5): ^1H nmr (deuteriochloroform): δ 1.31 and 1.32 (2s, 3H, $2-\text{CH}_3$), 1.44 and 1.45 (2s, 3H, $2-\text{CH}_3$), 1.67 and 1.68 (2s, 3H, $\text{C}\equiv\text{C-CH}_3$), 1.71 and 1.72 (2s, 3H, $\text{C}\equiv\text{C-CH}_3$), 1.77 (2d, 2H, $J = 2.9$ Hz, $3-\text{CH}_2$), 2.57 (2s, 1H, $\text{CH}\equiv$), 6.78 and 6.80 (2d, 1H, $J = 2.4$ Hz, H_8), 6.74 and 6.83 (2dd, 1H, $J = 2.4$ Hz, 8.4 Hz, H_6), 7.06 (bs, 1H, $2,3-\text{di-ClPh-CH}=\text{C}$), 7.15 and 7.30 (m, 3H, $2,3-\text{di-ClPh}$), 7.39 and 7.60 (2d, 1H, $J = 8.4$ Hz, H_5). IR (KBr) cm^{-1} : 3380 ($\equiv\text{C-H}$), 2128 ($\text{C}\equiv\text{C}$), MS m/z (%): 403 ($\text{M}^+ + 3$, 15), 402 ($\text{M}^+ + 2$, 65), 401 ($\text{M}^+ + 1$, 24), 400 (M^+ , 95), 384 (69), 319 (98), 255 (21), 251 (17), 177 (20), 175 (70), 158 (100), 134 (52), 91 (47). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{O}_2$: C, 68.83; H, 5.53. Found: C, 68.53; H, 5.85.

4-(2-Chlorobenzylidene)-2,2-dimethyl-7-(2-methylbut-3-yn-2-yloxy)-3,4-dihydro-2H-chromene (8e). A colorless oil (85%) as *E* and *Z* mixture (65:35): ^1H nmr (deuteriochloroform): δ 1.32 and 1.33 (2s, 3H, $2-\text{CH}_3$), 1.43 and 1.44 (2s, 3H, $2-\text{CH}_3$), 1.67 and 1.68 (2s, 3H, $\text{C}\equiv\text{C-CH}_3$), 1.71 and 1.72 (2s, 3H, $\text{C}\equiv\text{C-CH}_3$), 1.77 and 1.78 (2d, 2H, $J = 3.0$ Hz, $3-\text{CH}_2$), 2.61 and 2.62 (2s, 1H, $\text{CH}\equiv\text{C}$), 6.72 and 6.77 (2d, 1H, $J = 2.4$ Hz, H_8), 6.78 and 6.84 (2dd, 1H, $J = 2.4$ Hz, 8.4 Hz, H_6), 7.10 (bs, 1H, $2-\text{ClPh-CH}=\text{C}$), 6.21 and 7.30 (m, 4H, $2-\text{ClPh}$), 7.45 and 7.59 (2d, 1H, $J = 8.4$ Hz, H_5). IR (KBr) cm^{-1} : 3300 ($\equiv\text{C-H}$), 2132 ($\text{C}\equiv\text{C}$), MS m/z (%): 368 ($\text{M}^+ + 2$, 3), 366 (M^+ , 10), 350 (10), 300 (45), 285 (100), 221 (11), 175 (16), 125 (18). *Anal.* Calcd. for $\text{C}_{23}\text{H}_{23}\text{ClO}_2$: C, 75.30; H, 6.32. Found: C, 75.35; H, 6.52.

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