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Palladium catalyzed reaction in aqueous DMF: synthesis of 3-alkynyl substituted flavones in the presence of prolinol☆

Manojit Pal,* Venkataraman Subramanian, Karuppasamy Parasuraman and Koteswar Rao Yeleswarapu*

Chemistry-Discovery Research, Dr Reddy's Laboratories Ltd, Bollaram Road, Miyapur, Hyderabad 500050, India

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Abstract—(*S*)-Prolinol facilitated the coupling reaction of terminal alkynes with 3-iodoflavone under palladium–copper catalysis in aqueous DMF affording a mild and convenient method for the synthesis of 3-alkynyl substituted flavones of potential biological interest.
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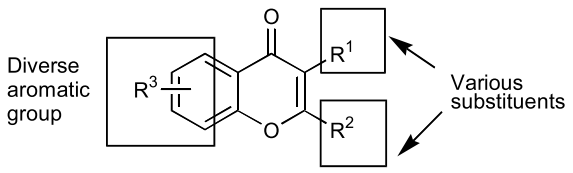
1. Introduction

3-Substituted flavones are of considerable interest because of their widespread occurrence in nature[1] as well as their profound biological activities.[2] They are also useful as antianaphylactic agents[3a] for the treatment of asthma, as potential cardio protective agents in doxorubicin antitumor therapy[3b] or as STS (steroid sulfatase) inhibitors for the possible treatment of a number of diseases including breast cancer.[3c] In continuation of our research under the new drug discovery program, we have recently reported the synthesis of various diarylheterocycles e.g. 3,4-diarylfuranones,[4a–c] 3,4-diarylmaleic anhydrides,[4d] 1,5-diarylpyrazoles[5] along with other heterocycles.[6] In further pursuance of our research on the development of novel anti-cancer agents we became interested in the synthesis of a combinatorial library based on the scaffold of flavones especially 3-alkenyl/alkynyl-substituted[7] flavones (**A**, Fig. 1) for their in vitro assay against various cancer cell lines. While the library model, as shown in Figure 1, has three centers for the introduction of diversity into flavone molecule, we initially focused on the modification of C-3 substituents. We postulated that attachment of an alkynyl moiety at the C-3 position of the flavone ring may lead to a novel class of compounds of potential biological significance, especially as inhibitors of thymidylate synthase (TS)—an essential enzyme required for the growth of cells.[7b]

Despite their biological importance only a few methods have been reported for the synthesis of 3-substituted flavones[3a,c,8] and none for the synthesis of 3-alkynyl substituted flavones. Over the last 25 years, palladium catalyzed coupling of terminal alkynes with the (hetro)aryl halide (the Sonogashira coupling)[9a] has become a most attractive and powerful tool for C–C bond formation reaction.[9b] The reaction is, in general, carried out with a large excess of a secondary or tertiary alkyl amine as a solvent/co-solvent and therefore, application of this protocol to large scale preparations often led to environmental pollution due to the volatile nature of these amines. Nevertheless, this palladium catalyzed reaction has been investigated extensively to improve the reaction conditions[9c–f] and the coupling reaction has been utilized successfully for the introduction of acetylenic moiety to various arenes and heteroarenes.[10] However, use of this methodology for the synthesis of 3-alkynyl flavones has not been explored previously.

The palladium catalyzed reaction in aqueous media has attracted much attention[11a–d] in recent time because water based synthetic processes are inherently safer as well as inexpensive. Therefore, the use of water-soluble catalysts as



A: R^1 = alkenyl, alkynyl

R^2 = aryl, heteroaryl; R^3 = H, NO_2, OCH_3 etc.

Figure 1. Diversity based flavone scaffold.

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Keywords: 3-alkynyl flavones; palladium catalyst; prolinol; aqueous media.
* Corresponding authors. Tel.: +91-40-2304-5439; fax: +91-40-23045438; e-mail: manojitpal@drreddys.com; fax: +91-40-23045007; e-mail: koteswarraoy@drreddys.com

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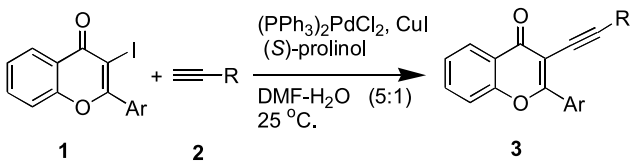
well as phosphine ligands e.g. sulfonated phosphines has been explored successfully. While the use of prolinol in the transition metal catalyzed Michael reaction in organic/aqueous media has been investigated,[11e,f] its use in palladium catalyzed reaction is not common. Moreover, unlike inorganic bases or primary amines, prolinol does not react with the flavone moiety[11g–i] and possesses ample water miscibility. Our continuing interest in palladium catalyzed reactions[12] prompted us to develop a mild and efficient method for the synthesis of 3-alkynyl substituted flavones via palladium catalyzed C–C bond formation reaction in aqueous media. Development of such a methodology could be beneficial for the synthesis of compounds having potential biological significance using iodoarenes that are sparingly soluble or insoluble in water.

2. Results and discussion

When 3-iodoflavone (**1**)[13a] was treated with an terminal alkyne (**2**, R=alkyl, hydroxyalkyl etc.)[13b] in aqueous dimethylformamide (DMF/H_2O; 5:1) in the presence of $(PPh_3)_2PdCl_2$ (0.05 equiv.), copper iodide (0.10 equiv.) and (*S*)-prolinol (4 equiv.) under a nitrogen atmosphere 3-alkynyl flavones (**3**, Scheme 1) were isolated as desired products. Results of this study are summarized in Table 1.



Scheme 1. Palladium catalyzed reaction of 3-iodoflavone with terminal alkynes.

The coupling reaction in aqueous DMF afforded desired products in good yields. By use of this palladium catalyzed reaction a variety of terminal acetylenes were reacted with 3-iodoflavone (Table 1). Various substituents (including alkyl, hydroxyl, phenyl etc.) present in the acetylenic compounds (**2**) were well tolerated during the course of the reaction and the yields were not affected drastically with the change of substituents in the acetylenic component (entries 1–4, Table 1). Yields were also found to be comparable irrespective of the nature of the aryl group present at the 2-position of the flavone moiety for a given alkyne when employed in the reaction (entries 5–8, Table 1).

The coupling reactions were usually carried out using $(PPh_3)_2PdCl_2$ as catalyst and CuI as a co-catalyst. However, the use of other palladium catalysts e.g. $(PPh_3)_4Pd$ and $Pd(OAc)_2/PPh_3$ was also examined and the reaction proceeded well in such cases (entries 4–5, Table 2). It is noteworthy that external addition of a phase transfer catalyst (PTC)[14a] or water soluble phosphine ligands[11b] are not required for the successful coupling reaction in the present case. To gain further evidence on the role of PPh_3, coupling reaction of **1a** with **2b** was carried out using $PdCl_2$ as catalyst under the same condition as indicated in Table 2. However, we failed to isolate the desired product **3b** perhaps due to the poor solubility of $PdCl_2$ in aqueous DMF. We therefore, investigated the use of relatively more water miscible palladium catalyst e.g. Na_2PdCl_4 in the same reaction and **3b** was isolated in moderate yield (~50%) when the reaction was carried out at higher temperature (60°C).

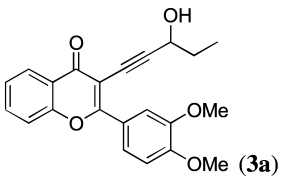
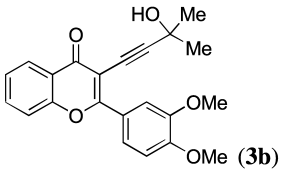
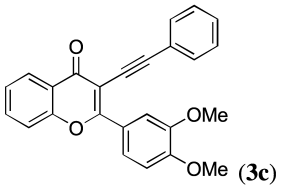
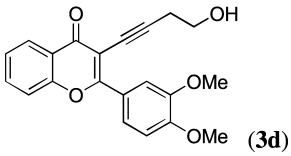
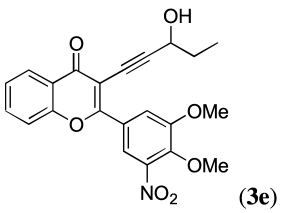
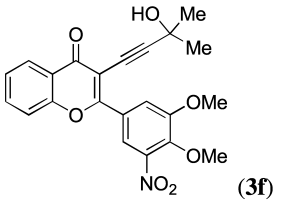
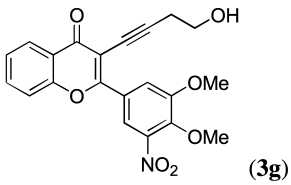
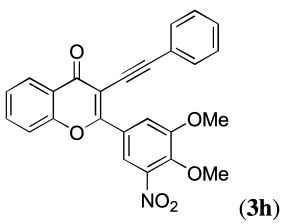
The coupling reaction of iodoflavone with terminal alkyne was carried out in DMF as a co-solvent because of its ability to dissolve the substrates as well as palladium/copper catalysts. Use of other co-solvent such as acetonitrile was found to be satisfactory (entry 3, Table 2) whereas, use of THF, dioxane was found to be less effective. Extensive studies were conducted to optimize the reaction conditions for the formation of **3** by varying the amount of added water. Use of 5:1 DMF/H_2O was found to be optimum as precipitation of reactants occurred in the presence of excess water.

While (*S*)-prolinol (bp 74–76°C/2 mm) was used as a base in the present cases, use of triethylamine (bp 88.8°C), the most widely used base in Sonogashira reaction, was also investigated (entry 1, Table 2). Due to the presence of the hydrophilic hydroxyl group (*S*)-prolinol was found to be more miscible with water than triethylamine, which therefore facilitated the coupling reaction in aqueous media affording better yields of products. Unlike ammonia use of excess prolinol did not affect the yield of product.[11c] Moreover, due to its lower volatility (thereby avoiding internal pressure development as well as ensuring its maximum recovery) and reactivity in compared to ammonia, prolinol has advantages over the other amine[15] and inorganic bases[11i] especially for the large scale preparations. The reactions were generally carried out under mild conditions i.e. at 25°C.

The present palladium catalyzed reaction of 3-iodoflavone with acetylenic compounds led to the formation of 3-alkynyl flavones in good yields. Interestingly, palladium mediated coupling of 3-iodoflavone with internal alkynes resulted in the formation of annulated products i.e. a mixture of benzo[*c*]xanthen-7-one and diphenylfuran derivatives[16a] due to the participation of the neighboring aryl group in the reaction cascades. The presence of inorganic base i.e. NaOAc and relatively strong reaction conditions (heating at 100°C for 72 h) was responsible for the opening of the flavone ring in such cases. It is noteworthy that no significant dimerization of terminal alkynes was observed during our synthesis of 3-alkynylflavones. This is in contrast to the earlier report on Sonogashira coupling of bromopyranone with terminal alkynes where 1,3-diynes were isolated as major products even in the absence of a stoichiometric additive.[16b] Perhaps terminal alkynes are more susceptible to undergo Pd–Cu mediated dimerization[16c] in the presence of triethylamine rather than prolinol.

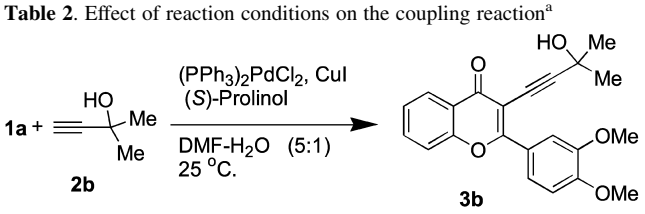
The palladium mediated coupling of 3-iodoflavone with terminal alkynes afforded cleaner products in the presence of prolinol when compared with that in the presence of triethylamine. Except few cases (entries 3, 4 and 8, Table 1) all products (**3**) isolated directly from the reaction mixture (after dilution with cold water) were often analytically pure and well characterized by their spectral (^1H NMR, ^{13}C NMR, IR, Mass) data. All the reactions were carried out

Table 1. Palladium catalyzed synthesis of 3-alkynyl substituted flavones in aqueous DMF[a]

Entry	Substrate (**1**) Ar=	Products[b] (**3**)	Yield (%)[c]
1	3,4-Dimethoxyphenyl (**1a**)	 (**3a**)	60
2	3,4-Dimethoxyphenyl (**1a**)	 (**3b**)	81
3	3,4-Dimethoxyphenyl (**1a**)	 (**3c**)	64
4	3,4-Dimethoxyphenyl (**1a**)	 (**3d**)	78[d]
5	3,4-Dimethoxy-5-nitrophenyl (**1b**)	 (**3e**)	59
6	3,4-Dimethoxy-5-nitrophenyl (**1b**)	 (**3f**)	52
7	3,4-Dimethoxy-5-nitrophenyl (**1b**)	 (**3g**)	77
8	3,4-Dimethoxy-5-nitrophenyl (**1b**)	 (**3h**)	72

[a] All reactions were carried out by using **1** (1.0 equiv.), **2** (3.0 equiv.), $(PPh_3)_2PdCl_2$ (0.05 equiv.), CuI (0.10 equiv.), prolinol (4 equiv.) in DMF/H_2O (5:1) for 12 h.
[b] Identified by ^1H NMR, ^{13}C NMR, IR, mass.
[c] Isolated yields.
[d] Reaction was carried out for 36 h.

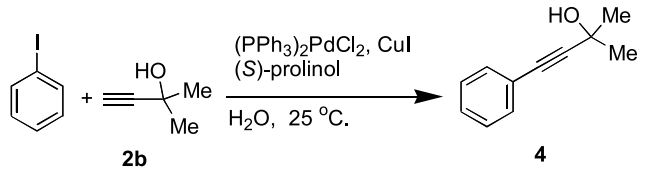
Table 2. Effect of reaction conditions on the coupling reaction[a]



Entry	Catalyst	Base (reaction time)	Yield (%)[b]
1	$(PPh_3)_2PdCl_2$	Et_3N (12 h)	46[c]
2	$(PPh_3)_2PdCl_2$	Prolinol (6 h)	81
3	$(PPh_3)_2PdCl_2$	Prolinol (12 h)	50[d]
4	$(PPh_3)_4Pd$	Prolinol (24 h)	80
5	$Pd(OAc)_2/PPh_3$	Prolinol (12 h)	75

[a] Reactions were carried out by using **1a** (1.0 equiv.), **2b** (3.0 equiv.), Pd catalyst (0.05 equiv.), CuI (0.10 equiv.), base (4 equiv.) in DMF/H_2O (5:1).
[b] Isolated yields.
[c] DMF/H_2O (10:1).
[d] Acetonitrile/H_2O (5:1).

using 5:1 DMF/H_2O as a solvent due to the poor solubility of 3-iodoflavone (**1**) in water alone. However, to asses the applicability of this methodology in water and considering iodoflavone as activated substrate for the present palladium-catalyzed reaction we investigated the coupling reaction of a more frequently used aryl halide such as iodobenzene with terminal alkyne **2b** at 25°C in water (Scheme 2). Iodobenzene was found to have good miscibility with water in the presence of prolinol and the reaction was completed within 30 min affording the desired product in good yield. This observation clearly indicates the high efficiency of the protocol when applied to the palladium catalyzed alkynylation of simple aryl iodides and therefore, the methodology has potential to be used widely in the synthesis of other internal alkynes via C–C bond formation reaction in aqueous media.[16d]



Scheme 2. Palladium catalyzed reaction of iodobenzene with terminal alkyne **2b** in water.

Mechanistically, these reactions seemed to proceed via generation of a Pd(0) complex e.g. $L_2Pd(0)$ according to the typical Sonogashira pathway.[9a] However, recent works by Amatore and Jutand provided strong evidence in support to the specific role played by halide ions to generate an anionic species such as $[L_2Pd(0)Cl]^-$.[17a,b] This anionic species generated from $Pd(PPh_3)_2Cl_2$ is thought to be the key intermediate and participates as active palladium species in these cross-coupling reactions.[17c] In the present case, presumably the prolinol stabilized anionic species (**A**) generated in situ (Scheme 3) facilitated the reaction in aqueous media due to its interaction with water molecules (via hydroxyl group of prolinol moiety of **A**).[17d] It is noteworthy that the palladium catalyzed cross-coupling reaction in the presence of other chelating ligands such as 2,2′-bipyridine or 2,2′:6′,2′-terpyridine has been reported earlier.[17c] Oxidative addition of the aryl iodide (**1**) to the zero-valent anion **A** affords the 18-electron complex **B** in which the chloride ion, borne by the Pd(0), remains attached to the Pd(II) center.[17e] PPh_3 being moderately donating (σ-donor) and accepting (π-acceptor) ligand would be expected to hold onto the electron rich palladium and therefore departure of prolinol is more likely rather than PPh_3 from **A** during its reaction with aryl iodide. The complex **B** then undergoes elimination of chloride ion in the presence of prolinol to yield a neutral pentacoordinated complex **C**. Nucleophilic displacement of the prolinol ligand of **C** by the terminal acetylene (**2**) gives an anionic pentacoordinated intermediate **D**, in which aryl and alkynyl ligands are at adjacent as well as favorable position for undergoing a fast reductive elimination reaction. 3-Alkynyl-flavone is thus obtained via reductive elimination followed by the regeneration of the active palladium species **A**′. The palladium species **A**′ then initiate the second (main) catalytic cycle (Scheme 3).

While the coupling reaction of 3-iodoflavone with terminal alkynes in the presence of $(PPh_3)_4Pd/CuI$ or $Pd(OAc)_2/PPh_3$ is expected to follow the same mechanistic pathway (Scheme 3), the anionic species (**A**) generated in these cases could be $[(PPh_3)_2Pd(0)X(prolinol)]^-$ where X=I [when $(PPh_3)_4Pd/CuI$ is used] or OAc [when $Pd(OAc)_2/PPh_3$ is used] depending on the nature of the catalysts employed in the coupling reaction.

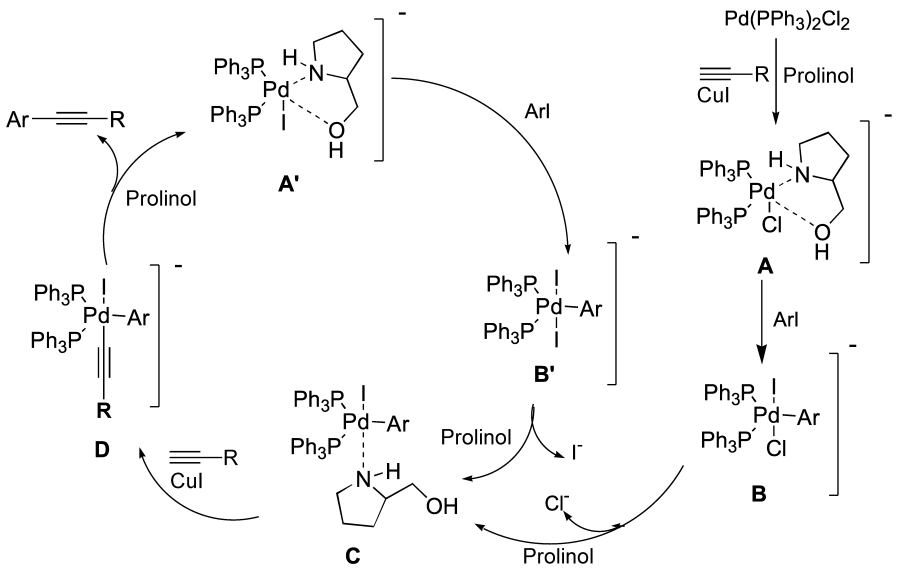
3. Conclusion

In conclusion, we have described a facile and mild palladium-mediated procedure for the synthesis of novel 3-alkynylflavones in the presence of prolinol in aqueous DMF. As far as we know, despite the report of employing various amines including aqueous ammonia no successful examples of Sonogashira coupling using prolinol have been reported. No significant side reaction such as dimerization of terminal alkynes or opening of the flavone ring was observed during the course of our reaction. The methodology can tolerate a variety of functional groups, dose not require the use of PTC/water soluble phosphine ligands and has potential to be utilized in water alone. Due to the operational simplicity as well as easy isolation and purification procedures for the products the methodology appears to be a useful alternative to the conventional Sonogashira reaction. Some of the compounds synthesized were tested for their pharmacological properties and a few of them showed interesting biological activities in vitro.[18] Further research is ongoing in our laboratory in order to extend the scope and generality of this methodology.

4. Experimental

4.1. General methods

Unless stated otherwise, reactions were performed under nitrogen atmosphere. Reactions were monitored by thin layer chromatography (TLC) on silica gel plates (60 F254; Merck), visualizing with ultraviolet light or iodine spray. Flash chromatography was performed on silica gel (SRL



Scheme 3. Possible mechanism for Pd-catalyzed reaction of iodoarene with terminal alkynes.

230–400 mesh) using distilled petroleum ether, ethyl acetate, dichloromethane, chloroform and methanol. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$, DMSO-d_6 or MeOH-d_4 solution on Varian Gemini 200 and 50 MHz spectrometers, respectively. Proton chemical shifts (δ) are relative to tetramethylsilane (TMS, δ=0.00) as internal standard and expressed in ppm. Spin multiplicities are given as s (singlet), d (doublet), t (triplet) and m (multiplet) as well as b (broad). Coupling constants (J) are given in hertz. Infrared spectra were recorded on a Perkin–Elmer 1650 FT-IR spectrometer. Melting points were determined using Buchi melting point B-540 apparatus and are uncorrected. Thermal analysis data [Differential Scanning Calorimetry (DSC)] was generated with the help of Shimadzu DSC-50 detector. MS spectra were obtained on a HP-5989A mass spectrometer. All the reagents used were from commercial sources and no further purification was performed.

4.2. General procedure for the preparation of iodoflavones

A mixture of flavone (1.0 mmol), iodine (1.10 mmol) and ceric ammonium nitrate (1.0 mmol) in acetonitrile (20 mL) was stirred at 65°C under nitrogen atmosphere for 5 h. The mixture was then poured into water (50 mL), extracted with ethyl acetate (3×25 mL). Organic layers were collected, combined, washed with cold sodium thiosulfate solution (2×10 mL) followed by water (2×30 mL), dried over Na_2SO_4 and concentrated under low vacuum. The crude compound thus obtained was purified by column chromatography to afford the iodo compounds as described below.

4.2.1. 2-(3,4-Dimethoxyphenyl)-3-iodo-4*H*-4-chromenone (1a). Yellow solid; yield 45 %, mp 152–154°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.27 (d, J=8.1 Hz, 1H); 7.72–7.68 (m, 1H), 7.52–7.35 (m, 4H), 7.01–6.97 (m, 1H), 3.97 (s, 3H, OMe), 3.96 (s, 3H, OMe); IR (KBr, cm^{-1}) 1640 (C=O), 1607, 1508; *m/z* (CI method) 409 (M+1, 100), 283 (70, M−I); ^{13}C NMR (50 MHz, $CDCl_3$) 174.48 (C=O), 164.1, 155.7, 151.2, 148.2, 134.0, 127.1, 125.7, 123.1, 119.8, 117.6, 117.5, 110.3, 107.5, 87.7 (CI=C), 56.9 (OMe), 56.6 (OMe). Elemental analysis found C, 50.18; H, 3.19; $C_{17}H_{13}IO_4$ requires C, 50.02; H, 3.21%.

4.2.2. 2-(3,4-Dimethoxy-5-nitrophenyl)-3-iodo-4*H*-4-chromenone (1b). Yellow solid; yield 15 %, mp 194–196°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.30 (d, J=7.8 Hz, 1H), 7.84 (s, 1H), 7.79–7.68 (m, 3H), 6.98 (s, 1H), 4.07 (s, 3H, OMe), 4.02 (s, 3H, OMe); IR (KBr, cm^{-1}) 1645 (C=O), 1520; *m/z* (CI method) 454 (M+1, 100); ^{13}C NMR (50 MHz, $CDCl_3$) 173.9 (C=O), 163.2, 153.7, 148.7, 148.7, 134.9, 134.2, 125.7, 124.8, 123.2, 121.7, 117.6, 112.9, 110.1, 88.8 (CI=C), 56.9 (OMe), 56.6 (OMe). Elemental analysis found C, 45.11; H, 2.50; $C_{17}H_{12}INO_6$ requires C, 45.06; H, 2.67%.

4.3. General procedure for the preparation of 3

A mixture of **1** (3 mmol), $(PPh_3)_2PdCl_2$ (0.15 mmol), CuI (0.3 mmol) and (*S*)-prolinol (12 mmol) in 5:1 DMF/H_2O (6 mL) was stirred at 25°C for 1 h under nitrogen atmosphere. The acetylenic compound **2** (9 mmol) was added slowly to the mixture with stirring. The reaction mixture was then stirred at 25°C according to the time indicated in Table 1. The mixture was poured into cold water (30 mL) with stirring and filtered (if solid was separated) or extracted with EtOAc (3×200 mL). Combined organic layers were washed with cold water (2×100 mL), dried over Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography (petroleum ether–EtOAc) to afford the desired product.

4.3.1. 2-(3,4-Dimethoxyphenyl)-3-(3-hydroxy-1-pentynyl)-4*H*-4-chromenone (3a). Yellow solid; yield 60 %; DSC 199°C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.25 (d, J=7.8 Hz, 1H), 7.87–7.80 (m, 2H), 7.72–7.69 (m, 1H), 7.53 (d, J=8.8 Hz, 1H), 7.46–7.42 (m, 1H), 6.99 (d, J=8.3 Hz, 1H), 4.62–4.60 (m, 1H, C*H*(OH)CH_2), 3.99 (s, 3H, OMe), 3.98 (s, 3H, OMe), 2.65–2.60 (bs, exchangeable with D_2O, OH), 1.84–1.79 (m, 2H, CH_2), 1.05 (t, J=7.8 Hz,

3H, CH_3); IR (KBr, cm^{-1}) 3419 (bs, OH), 1628 (C═O); *m/z* (CI method) 365 (M+1, 100); UV (MeOH, nm) 347.5, 251, 205; HPLC: 96.16 %. INERTSIL ODS 3V, KH_2PO_4/CH_3CN, 1 mL/min, 251 nm, retention time 29.35 min. Elemental analysis found C, 72.49; H, 5.55; $C_{22}H_{20}O_5$ requires C, 72.52; H, 5.53%.

4.3.2. 2-(3,4-Dimethoxyphenyl)-3-(3-hydroxy-3-methyl-1-butynyl)-4*H*-4-chromenone (3b). Light brown solid; yield 81 %; DSC 185.5°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.23 (d, *J*=8.1 Hz, 1H), 7.87 (d, *J*=8.3 Hz, 1H), 7.77–7.67 (m, 1H), 7.54–7.39 (m, 3H), 6.99 (d, *J*=8.6 Hz, 1H), 4.00 (s, 3H, OMe), 3.98 (s, 3H, OMe), 2.8 (bs, exchangeable with D_2O, OH), 1.62 (s, 6H, CH_3); IR (KBr, cm^{-1}) 3419 (bs, OH), 1626 (C═O), 1595; *m/z* (CI method) 365 (M+1, 40), 347 (100, –OH); ^{13}C NMR ($CDCl_3$, 50 MHz) 192.6, 159.9, 155.5, 153.6, 148.9, 131.9, 131.0, 130.2, 125.5, 122.3, 120.4, 119.5, 119.2, 111.8, 109.8, 107.1, 77.6, 68.7 (*C*(OH)Me_2), 56.0 (OMe), 55.9 (OMe), 28.6 (2C, Me); UV (MeOH, nm) 349, 252, 207; HPLC: 97.38%. INERTSIL ODS 3V, KH_2PO_4/CH_3CN (55:45), 1.0 mL/min, 252 nm, retention time 15.03 min. Elemental analysis found C, 72.58; H, 5.50; $C_{22}H_{20}O_5$ requires C, 72.52; H, 5.53%.

4.3.3. 2-(3,4-Dimethoxyphenyl)-3-(2-phenyl-1-ethynyl)-4*H*-4-chromenone (3c). Light brown solid; yield 64 %; DSC 228°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.24 (d, *J*=7.8 Hz, 1H), 7.92–7.88 (m, 2H), 7.75–7.68 (m, 1H), 7.57–7.31 (m, 7H), 7.03 (d, *J*=8.1 Hz, 1H), 3.99 (s, 3H, OMe), 3.89 (s, 3H, OMe); IR (Neat, cm^{-1}) 1630 (C═O), 1600; *m/z* (CI method) 383 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 176.5, 155.3, 151.2, 148.3, 133.8, 131.5, 128.8, 128.4, 128.3 (2C), 126.0, 125.4, 124.7, 124.0, 123.1, 122.7, 122.0, 117.8, 111.8, 110.5, 105.9, 98.1, 82.4, 55.9 (2C, OMe); UV (MeOH,nm) 355, 285, 250, 206; HPLC: 98%. INERTSIL ODS 3V, KH_2PO_4/CH_3CN, 1 mL/min, 250 nm, retention time 42.02 min. Elemental analysis found C, 78.56; H, 4.60; $C_{25}H_{18}O_4$ requires C, 78.52; H, 4.74%.

4.3.4. 2-(3,4-Dimethoxyphenyl)-3-(4-hydroxy-1-butynyl)-4*H*-4-chromenone (3d). Semisolid; yield 78 %; ^{1}H NMR (200 MHz, $CDCl_3$) 8.25 (d, *J*=7.8 Hz, 1H), 7.93–7.88 (m, 2H), 7.75–7.63 (m, 1H), 7.55–7.39 (m, 2H), 7.01 (d, *J*=8.3 Hz, 1H), 3.99 (s, 6H, OMe), 3.86 (t, *J*=5.4 Hz, 2H, CH_2), 2.75 (t, *J*=5.9 Hz, 2H, CH_2), 2.2–2.01 (bs, exchangeable with D_2O, OH); IR (KBr, cm−^{1}) 3417 (bs, OH), 1616 (C═O), 1551; *m/z* (CI method) 351 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 177.5, 164.3, 155.2, 151.8, 148.4, 128.6, 128.3, 125.9, 125.4, 122.6, 122.0, 117.8, 116.5, 110.7, 110.5, 105.7, 98.2, 60.6 (CH_2OH), 56.0 (OMe), 55.9 (OMe), 24.6 (CH_2). Elemental analysis found C, 72.08; H, 5.10; $C_{21}H_{18}O_5$ requires C, 71.99; H, 5.18%.

4.3.5. 2-(3,4-Dimethoxy-5-nitrophenyl)-3-(3-hydroxy-1-pentynyl)-4*H*-4-chromenone (3e). Yellow solid; yield 59%; DSC 195.9°C; ^{1}HNMR (200 MHz, $CDCl_3$) 8.27 (d, *J*=7.8 Hz, 1H), 7.76–7.62 (m, 2H), 7.49–7.38 (m, 2H), 7.21 (s, 1H), 4.43 (t, *J*=6.4 Hz, 1H, C*H*(OH)CH_2), 4.04 (s, 3H, OMe), 4.02 (s, 3H, OMe), 2.6–2.21 (bs, exchangeable with D_2O, OH), 1.68–1.59 (m, 2H, CH_2), 0.85 (t, *J*=7.5 Hz, 3H, CH_3); IR (KBr, cm^{-1}) 3424 (bs, OH), 1643 (C═O), 1579; *m/z* (CI method) 410 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 176.3, 164.9, 155.6, 152.8, 150.4, 140.5, 134.3, 128.6, 126.0, 125.8, 122.3, 121.5, 117.9, 113.0, 107.8, 99.8, 75.3, 63.7 (*C*(OH)CH_2), 56.8 (OMe), 56.6 (OMe), 30.3 (CH_2), 9.2 (Me); HPLC: 94.13 % INERTSIL ODS 3V, KH_2PO_4/CH_3CN, 1 mL/min, 246 nm, retention time=19.32 min. Elemental analysis found C, 64.58; H, 4.61; $C_{22}H_{19}NO_7$ requires C, 64.55; H, 4.68%.

4.3.6. 2-(3,4-Dimethoxy-5-nitrophenyl)-3-(3-hydroxy-3-methyl-1-butynyl)-4*H*-4-chromenone (3f). Light brown solid; yield 52%; DSC 183.4°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.26 (d, *J*=7.3 Hz,1H), 7.75–7.66 (m, 2H), 7.55–7.39 (m, 2H), 7.21 (s, 1H), 4.04 (s, 3H, OMe), 4.03 (s, 3H, OMe), 2.66 (bs, exchangeable with D_2O, OH), 1.44 (s, 6H, Me); IR (KBr, cm^{-1}) 3415.3 (bs, OH), 1649 (C═O), 1567; *m/z* (CI method) 410 (M+1, 40), 392 (70, –OH), 352 (100); ^{13}C NMR ($CDCl_3$, 50 MHz) 176.1, 164.6, 155.6, 152.7, 150.3, 133.9, 128.6, 125.9, 125.8, 122.9, 117.9, 117.8, 112.9, 111.7, 107.7, 103.4, 72.6, 65.0 (*C*(OH)Me_2), 56.8 (OMe), 56.6 (OMe), 30.9 (2C, Me); HPLC: 92.25 % INERTSIL ODS 3V, KH_2PO_4/CH_3CN, 1 mL/min, 246 nm, retention time=17.86 min. Elemental analysis found C, 64.61; H, 4.62; $C_{22}H_{19}NO_7$ requires C, 64.55; H, 4.68%.

4.3.7. 2-(3,4-Dimethoxy-5-nitrophenyl)-3-(4-hydroxy-1-butynyl)-4*H*-4-chromenone (3g). Yellow solid; yield 77 %; DSC 195.4°C; ^{1}H NMR (200 MHz, $CDCl_3$) 8.28 (d, *J*=7.8 Hz, 1H), 7.76–7.66 (m, 2H), 7.49–7.39 (m, 2H), 7.20 (s, 1H), 4.05 (s, 3H, OMe), 4.02 (s, 3H, OMe), 3.71 (t, *J*=5.9 Hz, 2H, CH_2), 2.58 (t, *J*=5.9 Hz, 2H, CH_2), 1.70 (bs, exchangeable with D_2O, OH); IR (Neat, cm^{-1}) 3424 (bs, OH), 1642 (C═O); *m/z* (CI method) 396 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 176.6, 164.3, 155.6, 152.8, 150.3, 140.6, 134.2, 125.9, 125.7, 122.2, 121.5, 117.9, 112.9, 107.7, 97.3, 77.6, 73.0, 60.5 (CH_2OH), 56.8 (OMe), 56.6 (OMe), 24.2 (CH_2); UV (MeOH, nm) 246, 255; HPLC: 92.67%, INERTSIL ODS 3V, KH_2PO_4/CH_3CN, 1 mL/min, 246 nm, retention time=31.52 min. Elemental analysis found C, 62.78; H, 4.40; $C_{21}H_{17}NO_7$ requires C, 63.80; H, 4.33%.

4.3.8. 2-(3,4-Dimethoxy-5-nitrophenyl)-3-(2-phenyl-1-ethynyl)-4*H*-4-chromenone (3h). Yellow Solid; yield 72 %, mp 110–112°C; ^{1}H NMR (200 MHz, $CDCl_3$), 8.3 (d, *J*=7.8 Hz, 1H), 7.79–7.67 (m, 2H), 7.51–7.29 (m, 8H), 4.06 (s, 3H, OMe), 3.97 (s, 3H, OMe); IR (KBr, cm^{-1}) 1650 (C═O), 1612, 1575; *m/z* (CI method) 428 (M+1, 100); ^{13}C NMR ($CDCl_3$, 50 MHz) 175.8, 164.5, 155.7, 152.7, 150.4, 140.8, 134.2, 133.9 (2C), 131.8, 128.8, 128.4 (2C), 128.2, 126.2, 125.8, 122.6, 121.8, 117.9, 113.1, 107.9, 98.0, 80.4, 56.8 (OMe), 56.7 (OMe); HPLC: 95 %, HICHROM RPB, KH_2PO_4/CH_3CN, 1 mL/min, 275 nm, retention time=39.60 min. Elemental analysis found C, 70.38; H, 4.10; $C_{25}H_{17}NO_6$ requires C, 70.25; H, 4.01%.

4.3.9. Palladium catalyzed reaction of iodobenzene with 2b in water. A mixture of iodobenzene (1.47 mmol), $(PPh_3)_2PdCl_2$ (0.15 mmol), CuI (0.15 mmol) and (*S*)-prolinol (3.7 mmol) in H_2O (3 mL) was stirred at 25°C for 30 min under nitrogen atmosphere. The acetylenic compound **2b** (3.7 mmol) was added slowly to the mixture with stirring. The reaction mixture was then stirred at 25°C for 20 min and diluted with EtOAc (200 mL), washed with cold 2N HCl (2×30 mL) followed by water (2×50 mL), dried over

anhydrous Na_2SO_4, filtered and concentrated under vacuum. The residue thus obtained was purified by column chromatography (petroleum ether–EtOAc) to afford 2-methyl-4-phenyl-3-butyn-2-ol[19] as light yellow solid in 85% yield, mp 52–54°C; ^{1}H NMR (200 MHz, $CDCl_3$): 7.46–7.41 (m, 2H) 7.33–7.27 (m, 2H), 1.94 (bs, exchangeable with D_2O, 1H), 1.64 (s, 6H); IR (KBr, cm^{-1}): 3357, 2982; MS (CI, *i*-butane): 143 (M^+-17, 100%); ^{13}C NMR: 131.5 (2C), 128.1 (2C), 128.0, 122.7, 93.9, 81.9, 65.4, 31.3 (2C).

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