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Synthesis, X-ray crystal structure and biological properties of acetylenic flavone derivatives

Roberto Artali [a], Pier Luigi Barili [b], Gabriella Bombieri [a,*], Paolo Da Re [a,1], Nicoletta Marchini [a], Fiorella Meneghetti [a], Piero Valenti [c]

[a] *Istituto di Chimica Farmaceutica e Tossicologica, Universita di Milano, Viale Abruzzi, 42, I-20131 Milan, Italy*
[b] *Dipartimento di Chimica Bioorganica e Biofarmacia, Via Bonanno, 33, I-56126 Pisa, Italy*
[c] *Dipartimento di Chimica Farmaceutica, Via Belmeloro, 6, I-40126 Bologna, Italy*

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Abstract

The reactions of iodoflavone with 3-methyl-3-hydroxybut-1-yne and 3-methylbut-3-en-2-yne are described and the antimicrobial and cytotoxic activities of the obtained compounds have been tested. The molecular structures of 6-(3-hydroxy-3-methylbut-1-ynyl)-flavone (**1a**) and 6-(3-methylbut-3-en-1-ynyl) flavone (**1b**) have been determined by X-ray crystallography. The planar configuration of the two compounds has been attributed to intramolecular hydrogen bond interactions. In **1a**, the presence of the hydroxyl group determines a dimeric arrangement of the molecules. In both compounds in the crystal state, molecular stacking has been observed.

Keywords: Flavone derivatives; Synthesis; X-ray structures; Antimicrobial and cytotoxic activities

1. Introduction

Since the discovery of the narcotic power of acetylene, the interest in the medicinal chemistry of alkyne has gradually increased. (Two exhaustive reviews [1,2] up dated the literature up to 1990.) From then on a number of interesting synthetic alkynes have been prepared, some of them have been obtained by introducing acetylenic group into a structure which has proved pharmacological activity (e.g. 5-ethynylnicotine [3], ethynylbenzodiazepine [4]), others which are totally synthetic (e.g. efevirenz [5], an HIV-1 reverse trascriptase inhibitor, C_2-alkynylated purines as cycline-dependent kinase (CDK) inhibitors [6]), without neglecting the continuous discovery of important, naturally occurring, acetylenic derivatives [7], which represent an important source for the design of new acetylenic types.

On the other hand the functionalization of flavone molecule, which is the structural unit of most flavonoids, is the counterpart of a number of biologically important derivatives. In this perspective a variety of functional groups, also borrowed from naturally occurring compounds, have been tested.

On the grounds of the above considerations and our interest in the medicinal chemistry of flavonoids [8,9], we thought of introducing some characteristic acetylene functions in the flavone molecule. In this perspective we selected two groups such as the 3-methyl-3-hydroxybut-1-ynyl (**a**) and the 3-methylbut-3-en-1-ynyl (**b**) (the former from a series of synthetic CDK inhibitors purine [6], the latter from phytotoxic fungal metabolites such as eutypine [10] and frustulosin [11]) to be inserted on to flavone nucleous.

* Corresponding author.
E-mail address: gabriella.bombieri@unimi.it (G. Bombieri).
[1] Passed away on March 6th, 2002. This paper is dedicated to the memory of his last contribution to this research.

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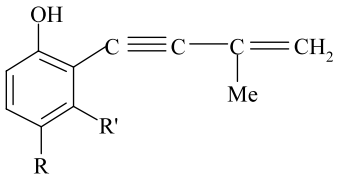
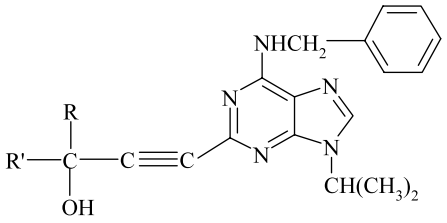


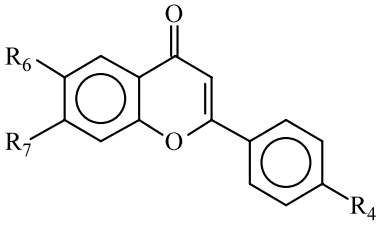
eutypine: R=CHO; R'=H

frustulosin: R=OH; R'=CHO

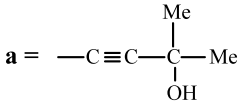


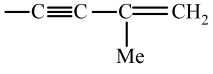
C_2 alkynylated purines

The following derivatives **1a**,**b**, **2a**,**b** and **3a**,**b** (see Scheme below) have been prepared by reacting 6-, 7- and 4′-iodoflavone with 3-methyl-3-hydroxybut-1-yne and 3-methylbut-3-en-1-yne according to Sonogashira reaction conditions [12], with good results.



R_6	R_7	R_4
1a	H	H
1b	H	H
H	**2a**	H
H	**2b**	H
H	H	**3a**
H	H	**3b**

a = 

b = 

1.1. Antimicrobial activity

The in vitro antimicrobial activity of compounds **1a**,**b**, **2a**,**b** and **3a**,**b** was investigated against pathogenic representative Gram positive (*S. aureus*, ATCC6538P) and Gram negative bacteria (*Escherichia choli*, ATCC 11105), yeasts (*C. albicans*, ATCC 10231, *C. lipolytica*, CBS 6124) and mould (Penicillium sp.). The minimal inhibitory concentrations (MICs) were determined by agar plate dilution method. Mueller–Hiton agar (BBL) and Sabouraud Dextrose Agar (Difco) were employed for bacterial and fungal growth, respectively. Inocula containing 10^5–10^6 CFU/ml of bacteria and 10^4–10^5 CFU/ml of fungi were prepared from broth cultures in log phase growth. Bacterial and fungal plates were made in triplicate and incubated at 37 and 28 °C for 48 and 72 h, respectively: only compound **3a** showed a low activity against all the fungal strains (MIC = 50 μg/ml). No antimicrobial activity was evidenced by the other derivatives.

1.2. Cytotoxic activity

The compounds were tested for direct cytotoxicity in a preliminary in vitro assay against three human tumor cell lines: LoVo from human colon adenocarcinoma, 2008 from human ovarian adenocarcinoma and MCF-7 from breast adenocarcinoma. All the compounds are inactive.

2. Results and discussion

Molecule **1a** is about planar. (Fig. 1 (top)) The presence of the hydroxyl moiety of the 3-hydroxy 3-methylbut-moiety terminal group, is essential to the molecular packing giving rise to an intermolecular

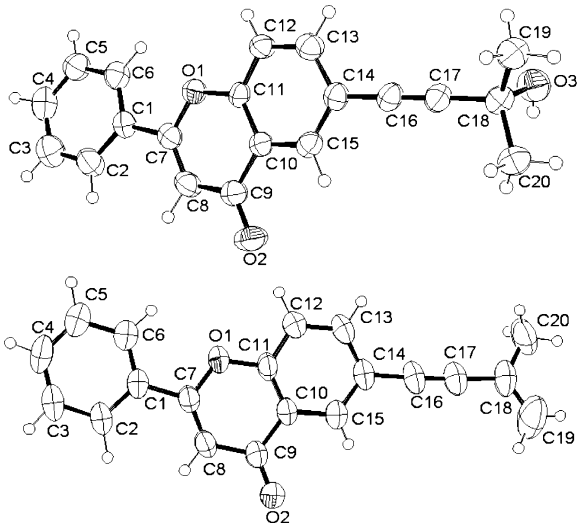


Fig. 1. ORTEP drawings of compound **1a** (top) and **1b** (bottom).

hydrogen bond between two molecules related by a crystallographic inversion centre, where O(3)–H is donor of a proton to the ketonic oxygen O(2) of the partner molecule the O(3)···O(2′) separation is 2.853(5) Å, with distance O(3)–H(3)···O(2′) 2.21(7) Å and angle of 148(6)° (′ at $1-x, 1-y, 1-z$) with 'dimer' formation

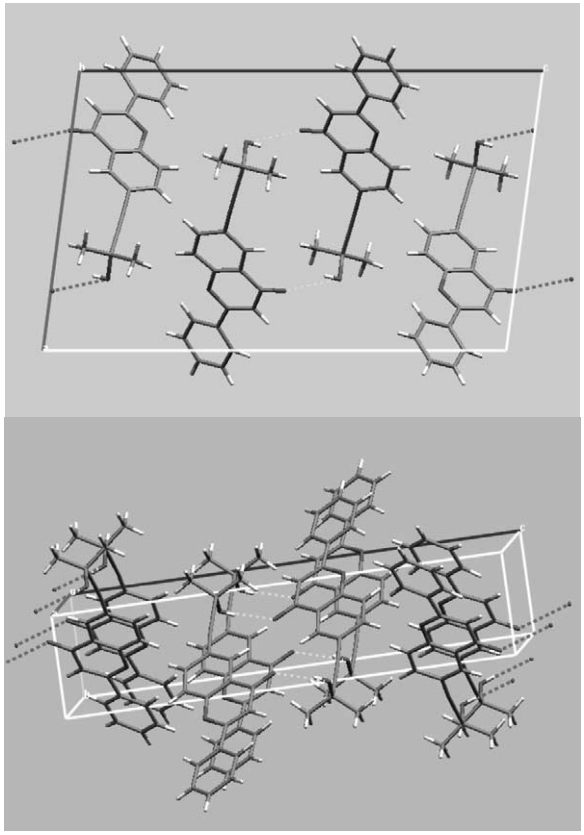


Fig. 2. Crystal packing of **1a** showing the dimers (top) and the dimer interactions (bottom). Dotted lines show the intermolecular interactions.

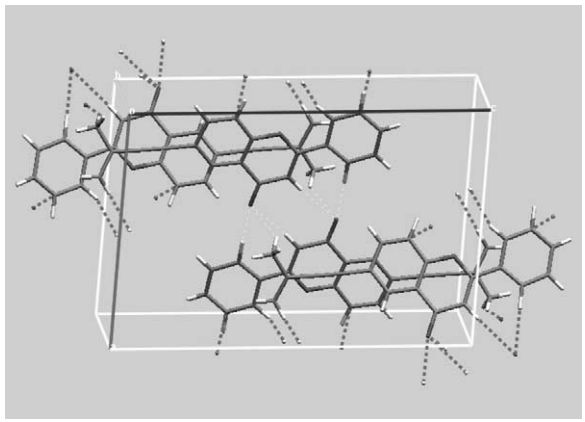


Fig. 3. Crystal packing of **1b** (the H-bond interactions are in dotted lines).

as described in Fig. 2 (top), which represents the crystal cell content. In addition the dimers are characterized by molecular stacking involving mainly the phenyls that are at a distance of about 3.5 Å along the *b* axis (Fig. 2 (bottom)).

The dihedral angle between the phenyl and the bicyclic moiety is 11.8(1)° (torsion C(6)–C(1)–C(7)–C(8) −166.6(5)°) reflects the major deviation from planarity of the molecule.

The acetylenic moiety is slightly shifted from the plane of the aromatic ring (C(10)→C(15)) with deviations C(16) −0.092(4), C(17) −0.292(4), C(18) −0.550(4), C(19) −0.271(4), C(20) −0.243(5) and O(3) −1.925(4).

Planar configurations of flavonoid structures are reported for acacetin and 5,6 benzoflavone through hydrogen bonds with the carbonyl oxygen atoms [13]. In 2′-methoxyflavone [14] the planarity of the phenyl ring with the benzopyrone plane has been attributed to two short intramolecular hydrogen contacts between proton of the phenyl and oxygen of the pyrone C–H···O in the order of 2.2 Å with angle of 100°. An intramolecular hydrogen bond interaction C(6)–H(6)···O(1) 2.29(4) Å angle 102(3)° possibly stabilizing the planarity is present also here.

The molecule of **1b** is also about planar. The best mean planes calculated on each of the two fused rings

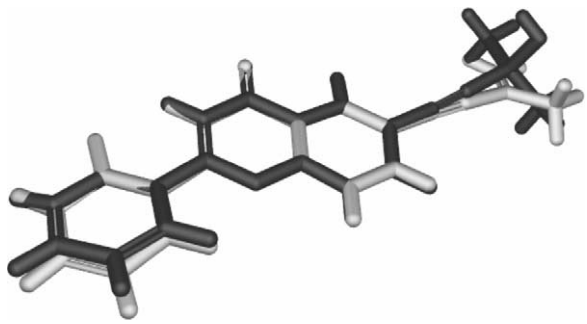
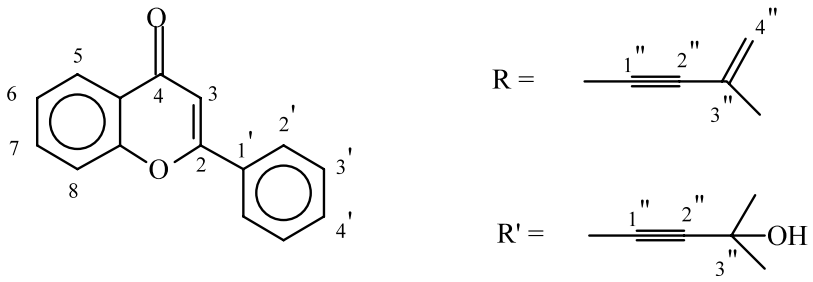


Fig. 4. Superimposition of the compound **1a** (dark grey) and **1b** (pale grey).

Table 1



^{1}H NMR data

	1a	1b	2a	2b	3a	3b
H-3	6.80	6.77	6.83	6.77	6.81	6.81
H-5	8.42	8.25	8.11	8.12	8.22	8.21
H-6			7.34	7.41	7.41	7.41
H-7	7.67	7.68			7.70	7.69
H-8	7.45	7.47	7.50	7.59	7.54	7.55
OH	3.0		3.1		3.6	
Me	1.66	1.99	1.67	2.01	1.66	2.01
Ar(o)	7.87	7.86	7.85	7.86	7.75	7.86
Ar(m+p)	7.51	7.49	7.52	7.50	7.45	7.56
H-4″a		5.43		5.48		5.46
H-4″b		5.34		5.40	7.96	5.37
$J_{5,6}$			8.21	8.21	1.45	7.96
$J_{5,7}$	2.11	2.09			0.36	1.50
$J_{5,8}$	0.45		0.38		7.00	
$J_{6,7}$					1.16	7.00
$J_{6,8}$			1.46	1.46	8.58	1.23
$J_{7,8}$	8.67	8.68				8.54
$J_{4'' \text{ gem}}$		1.81		1.82		1.93

show planarity for both, the -3-en-1-ynyl moiety is also rather planar with deviations in the range −0.009(4)–0.010(8) Å and it is bent with respect to the adjacent aromatic moiety of 21.4(2)°, while the phenyl group attached to the fused ring system is slightly rotated to the bicyclic system of −175.5(3)° (torsion angle considered C2–C1–C7–O1). An ORTEP [15] view of the molecule with the atom numbering scheme is in Fig. 1 (bottom).

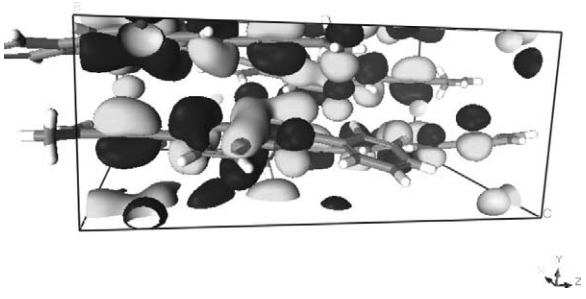


Fig. 5. HOMO molecular orbital distribution into the cell of compound **1b** (negative parts in black, positive in pale grey).

Table 2
^{13}C NMR data

	1a	1b	2a	2b	3a	3b
C-2	163.43	163.27	163.53	163.24	162.53	162.42
C-3	107.51	107.42	107.69	107.55	107.61	107.64
C-4	177.57	177.35	177.91	177.55	178.44	178.18
C-4a	123.63	123.67	123.24	123.11	123.75	123.86
C-5	128.99	128.82	125.59	125.45	125.67	125.63
C-6	120.27	120.58	128.33	128.16	125.31	125.22
C-7	136.49	136.29	128.71	120.90	133.90	133.77
C-8	118.20	118.21	120.91	120.67	117.97	117.97
C-8a	155.47	155.37	155.74	155.67	156.08	156.10
C-1′	131.36	131.31	131.43	131.36	130.86	130.93
C-2′	126.21	126.10	126.22	126.07	125.92	126.00
C-3′	128.99	126.10	129.03	128.90	132.04	132.01
C-4′	131.70	131.60	131.73	131.36	126.33	126.43
C-1″	80.45	86.70	80.51	86.70	81.00	87.48
C-2″	95.12	91.50	98.07	94.22	97.38	93.55
C-3″	65.38	126.38	65.41	126.07	65.31	126.67
C-4″		122.38		123.53		122.99
CH_3	31.37	23.21	31.27	23.07	31.31	23.23

The molecular packing reported in Fig. 3 shows molecular stacking for the molecules that two by two are facing. The interaction involves the triple bond of one molecule and the bicyclic system of the other, with separations from C(16)···C(10)′ 3.676(5) Å, C(16)···C(9) 3.484(5) Å, C(17)···C(8) 3.607(5) Å and C(17)···C(9) 3.594(5) Å (′ at $1.5-x$, $1/2+y$, $1.5-z$). A contribution to the molecular cohesion among the couple involved in molecular stacking is also given by the intermolecular contacts C(6)–H(6)···O(2)″ 2.33(4) Å angle 173(3)° and C(8)–H(8)···O(2)″ 2.56(3) Å angle 174(3)° (″ at $2-x$, $-y$, $2-z$).

The C(6)–H(6)···O(1) 2.29(4) Å intramolecular distance with angle of 100(3)°, again contributes to the nearly coplanarity of the phenyl ring with the rest of the molecule.

The bond lengths and angles of the two molecules are very similar except for the acetylenic moiety, in fact in **1b** the double bond between C(18)–C(19) (1.344(7) Å) seems to be delocalized with shortening of the adjacent C(18)–C(20) (1.428(6) Å) and C(17)–C(18) (1.443(5) Å) bond distances, while in **1a** the corresponding C(17)–C(18) bond distance, in absence of resonance effects, maintains the usual value of 1.490(6) Å. The bending of the two groups is also different being the angle C(14)–C(16)–C(17) of 173.2(5)° in **1a** and 177.4(4)° in **1b** as it is shown in Fig. 4 which represents the superimposition of the two molecules. This difference could be related to the different packing of the two molecules, with the formation of 'dimers', through the hydrogen bond interaction previously described for **1a**, forcing the molecular bending in some way. The molecular stacking of the terminal phenyls in **1a** could also explain the difference in the dihedral angle with the benzopyran moiety 11.8(1)° in **1a** versus 4.5(3)° in **1b**.

2.1. Modeling studies

An electronic structure analysis of **1b** was carried out starting from the crystallographic coordinates. The program GULP [16] was used to obtain charge distribution, electric field and electrostatic potential into the cell. The cell content was analysed by GAMESS-US [17] in order to have more detailed information about the electronic distribution and molecular orbitals (HOMO and LUMO).

The results of these calculations are reported in Fig. 5, where it is shown as the observed crystal packing can be related to the HOMO topology, where the superimposition of two adjacent molecules represents a minimum energy condition.

3. Experimental

3.1. Chemistry

All m.p. were determined in open glass capillaries using a Büchi apparatus and are uncorrected. NMR spectra were performed with a Bruker AC200 instrument operating at 200 MHz. The ^{1}H NMR and ^{13}C NMR data of compound **1a**,**b**, **2a**,**b** and **3a**,**b** are reported in Tables 1 and 2, respectively.

3.1.1. 6-(3-Hydroxy-3-methylbut-1-ynyl)-flavone (*1a*)

A mixture od 6-iodoflavone (0.35 g, 1 mmol), K_2CO_3 (1 g), CuI (0.02 g), PPh_3 (0.0062 g, 1 mmol) and 10% Pd/C (0.106 g, 1 mmol) in 1:1 DME/H_2O (12 ml) was stirred at room temperature (r.t.) for 30 min and then 3-methyl-3-hydroxybut-1-yne (0.28 ml, 2.61 mmol) were added. The mixture was gently refluxed for 15 h, cooled and filtered (celite). The filtrate was extracted three times with EtOAc, washed with water, dried and evaporated to dryness. The crude product was purified by flash chromatography on silica gel, eluting with 1:1 hexane–EtOAc: 0.25 g of white product, m.p. 187–190 °C, were

Table 3
Crystal data and structure refinement for **1a** and **1b**

	Comp. **1a**	Comp. **1b**
Empirical formula	$C_{20}H_{16}O_3$	$C_{20}H_{14}O_2$
Formula weight	304.33	286.31
Temperature (K)	293(2)	293(2)
Wavelength (Å)	0.71073	0.71073
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$ (14)	$P2_1/n$ (14)
Unit cell dimensions		
a (Å)	13.602(3)	11.684(2)
b (Å)	5.113(3)	7.380(1)
c (Å)	22.462(5)	17.569(3)
β (°)	97.5(4)	93.9(3)
V (Å^3)	1548.8(10)	1511.4(4)
Z	4	4
D_{Calcd} (Mg/m^3)	1.305	1.258
Absorption coefficient (mm^{-1})	0.087	0.080
$F(000)$	640	600
Crystal size(mm)	0.6 × 0.5 × 0.7	0.4 × 0.4 × 0.3
2θ Range (°)	3.02–27.00	2.99–26.02
Limiting ind.	$-16=h=16$, $-1=k=6$, $-1=l=26$	$-14=h=14$, $0=k=9$, $0=l=21$
Reflection collected/unique	4109/3159	2544/2462
Refinement method	full-matrix least-squares on F^2	
Data/restraints/parameters	3159/0/250	2462/0/244
Final R indices [$I > 2\sigma(I)$]	$R_1=0.0452$, $wR_2=0.0886$	$R_1=0.0876$, $wR_2=0.1811$
Goodness-of-fit on F^2	0.897	1.299
Largest difference peak and hole (e Å^{-3})	0.188 and −0.196	0.190 and −0.228

Table 4
Bond lengths (Å) and angles (°) for **1a** and **1b**

	Compound **1a**	Compound **1b**
Bond length (Å)		
O(1)–C(7)	1.362(5)	1.362(4)
O(1)–C(11)	1.375(4)	1.376(3)
O(2)–C(9)	1.244(4)	1.227(4)
O(3)–C(18)	1.444(5)	
C(1)–C(2)	1.381(6)	1.385(5)
C(1)–C(6)	1.387(6)	1.367(5)
C(1)–C(7)	1.485(6)	1.485(4)
C(2)–C(3)	1.380(7)	1.396(5)
C(3)–C(4)	1.368(7)	1.346(7)
C(4)–C(5)	1.362(7)	1.360(6)
C(5)–C(6)	1.390(6)	1.393(5)
C(7)–C(8)	1.343(5)	1.323(4)
C(8)–C(9)	1.437(6)	1.450(4)
C(9)–C(10)	1.455(5)	1.463(4)
C(10)–C(11)	1.391(5)	1.366(4)
C(10)–C(15)	1.397(6)	1.406(4)
C(11)–C(12)	1.372(5)	1.386(5)
C(12)–C(13)	1.367(6)	1.381(5)
C(13)–C(14)	1.414(5)	1.393(5)
C(14)–C(15)	1.383(5)	1.373(5)
C(14)–C(16)	1.434(6)	1.438(4)
C(16)–C(17)	1.187(6)	1.188(4)
C(17)–C(18)	1.490(6)	1.443(5)
C(18)–C(19)	1.502(5)	1.344(7)
C(18)–C(20)	1.520(5)	1.428(6)
Bond angles (°)		
C(7)–O(1)–C(11)	119.7(3)	119.1(3)
C(2)–C(1)–C(6)	119.3(5)	119.5(3)
C(2)–C(1)–C(7)	120.5(4)	120.4(3)
C(6)–C(1)–C(7)	120.2(4)	120.2(3)
C(3)–C(2)–C(1)	119.9(6)	118.5(4)
C(4)–C(3)–C(2)	121.0(6)	121.6(4)
C(5)–C(4)–C(3)	119.4(6)	119.9(4)
C(4)–C(5)–C(6)	121.0(6)	119.9(5)
C(1)–C(6)–C(5)	119.4(5)	120.4(4)
C(8)–C(7)–O(1)	121.7(4)	122.4(3)
C(8)–C(7)–C(1)	126.5(4)	126.9(3)
O(1)–C(7)–C(1)	111.8(4)	110.6(3)
C(7)–C(8)–C(9)	122.5(5)	122.4(3)
O(2)–C(9)–C(8)	123.6(4)	123.4(3)
O(2)–C(9)–C(10)	121.6(4)	122.6(3)
C(8)–C(9)–C(10)	114.8(4)	113.9(3)
C(11)–C(10)–C(15)	117.9(4)	117.8(3)
C(11)–C(10)–C(9)	119.7(4)	120.2(3)
C(15)–C(10)–C(9)	122.3(4)	122.0(3)
C(12)–C(11)–O(1)	116.6(4)	115.5(3)
C(12)–C(11)–C(10)	121.8(4)	122.6(3)
O(1)–C(11)–C(10)	121.5(4)	121.9(3)
C(13)–C(12)–C(11)	119.1(5)	118.4(4)
C(12)–C(13)–C(14)	121.8(5)	120.8(3)
C(15)–C(14)–C(13)	117.3(5)	119.3(3)
C(15)–C(14)–C(16)	121.2(4)	121.4(3)
C(13)–C(14)–C(16)	121.5(4)	119.3(3)
C(14)–C(15)–C(10)	121.9(4)	121.1(3)
C(17)–C(16)–C(14)	173.2(5)	177.4(4)
C(16)–C(17)–C(18)	179.2(5)	178.1(5)
O(3)–C(18)–C(17)	109.5(4)	
O(3)–C(18)–C(19)	105.8(4)	
C(17)–C(18)–C(19)	110.0(4)	119.2(5)
O(3)–C(18)–C(20)	110.7(4)	
C(17)–C(18)–C(20)	109.0(4)	118.0(4)
C(19)–C(18)–C(20)	111.8(4)	122.8(4)

obtained. *Anal*. for $C_{20}H_{16}O_3$: Calc.: C, 78.94; H, 5.26; Found: C, 78.84; H, 5.21%.

*3.1.2. 7-(3-Hydroxy-3-methylbut-1-ynyl)-flavone (**2a**)*

With the same procedure starting from 7-iodoflavone (1 g, 2.87 mmol), 0.85 g of white crystalline product, m.p. 138–140 °C (EtOAc), were obtained. *Anal*. for $C_{20}H_{16}O_3$: Calc.: C, 78.94; H, 5.26; Found: C, 78.80; H, 5.19%.

*3.1.3. 4′-(3-Hydroxy-3-methylbut-1-ynyl)-flavone (**3a**)*

With the same procedure starting from 4′-iodoflavone (1 g, 2.87 mmol), 0.45 g of white crystalline product, m.p. 105–108 °C (EtOAc), were obtained. *Anal*. for $C_{20}H_{16}O_3$: Calc.: C, 78.94; H, 5.26; Found: C, 79.02; H, 5.22%.

*3.1.4. 6-(3-Methylbut-3-en-1-ynyl)-flavone (**1b**)*

A mixture of 6-iodoflavone (1 g, 2.87 mmol), 3-methylbut-3-en-2-yne (0.95 ml), $Pd(PPh_3)_2Cl_2$ (0.02 g) and CuI (0.006 g) in $NHEt_2$ (20 ml) was stirred overnight at r.t.. After evaporation, the residue was treated with $CHCl_3$. The organic layer was washed in dil HCl, water, dried and evaporated. The crude product was purified by crystallization from EtOAc to afford 0.85 g of product m.p. 123–126 °C. *Anal*. for $C_{20}H_{14}O_2$: Calc.: C, 83.91; H, 5.00; Found: C, 83.65; H, 5.12%.

*3.1.5. 7-(3-Methylbut-3-en-1-ynyl)-flavone (**2b**)*

With the same procedure, starting from 7-iodoflavone (1 g, 2.87 mmol), 0.65 g of white crystalline product, m.p. 110–112 °C (EtOAc), were obtained. *Anal*. for $C_{20}H_{14}O_2$: Calc.: C, 83.91; H, 5.00; Found: C, 83.88; H, 5.06%.

*3.1.6. 4′-(3-Methylbut-3-en-1-ynyl)-flavone (**3b**)*

With the same procedure, starting from 4′-iodoflavone (1 g, 2.87 mmol), 0.55 g of white crystalline product, m.p. 134–136 °C (EtOAc), were obtained. *Anal*. for $C_{20}H_{14}O_2$: Calc.: C, 83.91; H, 5.00; Found: C, 83.80; H, 5.08%.

3.2. X-ray crystallography

Crystals of compounds **1a** and **1b** were grown by slow evaporation of a EtOAc solution. A suitable single crystal for both compounds was mounted on a glass fiber on a CAD4 diffractometer with graphite monochromated MoKα radiation (λ 0.71073 Å). The cell parameters were determined and refined by least-

squares fit of 20 high angle reflections. The structures were solved by direct methods using SIR-92 [18] and conventional Fourier synthesis (SHELX-97 [19]). The refinement of the structures was made by full matrix least-squares on F^2. All non-H-atoms were refined anisotropically. The H-atoms positions were in part obtained by a close examination of a final difference Fourier and the remaining ones, introduced at calculated positions and refined with fixed isotropic thermal parameters (1.2 U eq of the parent atom). The summary of the crystal data and refinement is given in Table 3 and bond lengths and angles for the two compounds are compared in Table 4.

4. Supplementary material

The supplementary crystallographic data have been deposited at the Cambridge Crystallographic Data Centre CCDC nos. 199687 and 199688 for compounds **1a** and **1b**. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB 2 1EZ, UK (fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac:uk).

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