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Synthesis and anti-tubulin evaluation of chromone-based analogues of combretastatins

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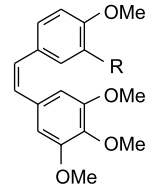
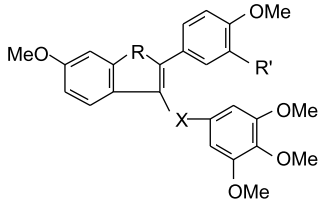
Abstract—Twenty new hybrid compounds with both combretastatin and flavone moieties were synthesized. These derivatives are classified according to the position of the trimethoxyphenyl ring at C-2 or C-3 of the chromone and presence or absence of a carbonyl as a linker between C-3 and the aryl ring. Most of these compounds were prepared from hesperidin or naringin, two natural and abundant *Citrus* flavonoids. Seven of these combretastatin analogues revealed anti-tubulin activity but in a medium range.

1. Introduction

Tubulin is a heterodimeric protein, which can exist as α,β-dimers and microtubules in a dynamic equilibrium. Polymerization into microtubules provides the main constituents of the mitotic spindle, which explains the crucial role of this protein in cellular division. Compounds that interfere with this equilibrium, either by stabilizing the microtubules or inhibiting their formation, are interesting as potential anticancer drugs.[1] So tubulin appears as a major target in this field of drugs discovery. Combretastatin A-4 (CA-4) **1** is a powerful inhibitor of tubulin polymerization (ITP) displaying cytotoxic and antivascular activities by binding at the colchicine site.[2] This natural stilbene, which was isolated from the bark of *Combretum caffrum* Kuntze, a South African bush willow tree, proved to be the most promising compound of the new class of combretastatins and was chosen as the model for the synthesis of hundreds of analogues.[3] Clear structure–activity relationships could be drawn from these synthesis, which display the importance for the bioactivity of: (a) the 3,4,5-trimethoxyphenyl ring (however, replacement by a 3,4,5-trimethylphenyl ring is not prejudicial);[4] (b) a 4′-methoxy substituted phenyl ring with or without a second substituent at C-3′ (removal of the 3′-OH or its substitution by an amino group result in compounds **2**[5] and **3**[6] with similar bioactivities as CA-4); (c) a *cis*-ethene bridge (isomerization of CA-4 and cis combretastatin analogues during storage and administration cause a reduction in both cytotoxicity and anti-tubulin activity).[7] This last point of the SAR studies led to the synthesis of many cis-restricted analogues with an ethene bridge as part of a heterocycle.[7] Although the most fruitful results were found among the substituted monocycle-bridged analogues,[8] compounds with a bicyclic system on the bridge, such as the indole **4**, displayed a strong bioactivity.[9] Furthermore, addition of a one-carbon linker (C═O) between the bicyclic system (indole, benzo[*b*]thiophene, benzo[*b*]furane) and the trimethoxyphenyl ring seemed to be favorable and sometimes essential for cytotoxicity and ITP (**6** active vs **5** inactive).[9,10]



R	
OH	**1**
H	**2**
NH_2	**3**



R	R'	X	
NH	OH	nothing	**4**
O	H	nothing	**5**
O	H	C=O	**6**

Keywords: Flavones; *Citrus* flavonoids; Combretastatins; Tubulin.
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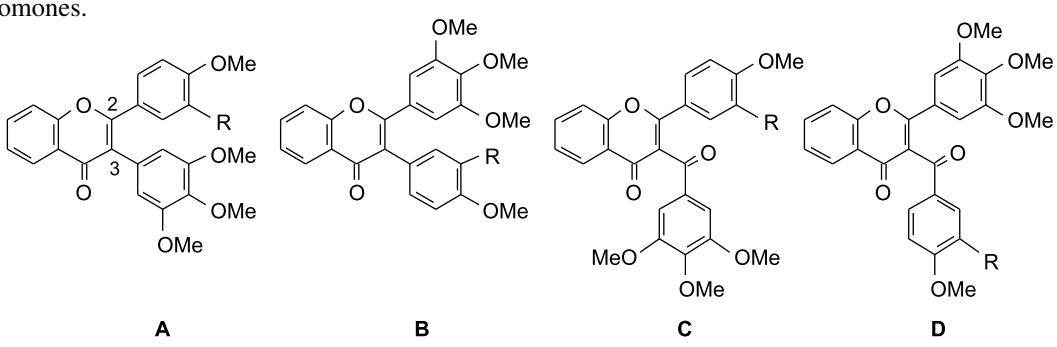
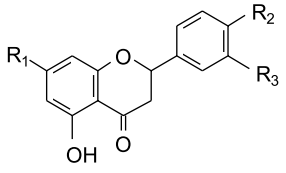
In order to enlarge the SAR studies of these bicyclic-bridged compounds, we have synthesized new analogues of combretastatins with the ethene bridge as part of a chromone. These new derivatives can be regarded as hybrid structures with both combretastatin and flavone moieties. This last point seemed of interest owing to the previously described cytotoxicity and antitubulin activity of some flavones.[11] All the chromone-based analogues related in this paper possess a substructure of combretastatins **1**, **2** or **3** and can be classified into four groups (**A**, **B**, **C**, **D** with R=H, OH or NH_2) according to the position of the trimethoxyphenyl ring at C-2 or C-3 of the chromone and presence or not of a C=O linker at C-3. They can also differ in the substitution pattern (unsubstituted or 5,7-disubstituted) of the chromone moiety. Unsubstituted flavones were prepared by total synthesis, while most of the 5,7-disubstituted ones were obtained by semisynthesis. By starting from some natural abundant flavonoids (vide infra), the second aim of this study was also to display the importance of such raw materials for an easy access to novel possibly interesting 2,3-diaryl chromones.



2. Results and discussion

2.1. Synthesis of analogues of the group A (24–32, 47 and 48)

We began our study by the group **A** because of the easy availability of two *Citrus* flavonoids, hesperidin **7** and naringin **8**, which have been used as starting materials for semisynthesis. **7** and **8** were chosen because of their adequate substitutions at C-3′ and C-4′ allowing access to analogues of combretastatins **1**, **2** and **3**. Compounds **24–31**, **47** and **48** substituted at C-5 and C-7 were prepared from **7** or **8**, while total synthesis provided the last one, **32**, unsubstituted on the chromone ring. For all the compounds, the trimethoxyphenyl ring was fixed at the C-3 carbon of the chromone by a Suzuki reaction between a 3-bromoflavone and 3,4,5-trimethoxybenzeneboronic acid.[12]



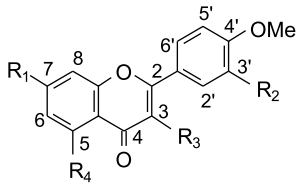
R_1	R_2	R_3	
O-rutinosyl	OMe	OH	**7**
O-neohesperidosyl	OH	H	**8**

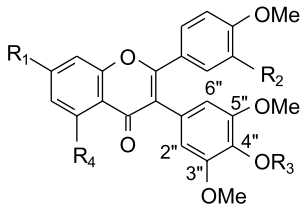
2.1.1. Analogues of combretastatin 1.

The synthesis of **24–29**, analogues of CA-4 **1** is shown in Scheme 1. Hesperidin **7** provided by a well-known process (I_2–pyridine)[13] the corresponding flavone, diosmin **9**, which led in three steps to 3-bromodiosmetin **12** via peracetyldiosmin **10** and its 3-bromo derivative **11**. It is worth noting that the prior peracetylation step is necessary for it allows regiospecific bromination at C-3 by deactivation of C-6 and C-8 (as previously reported, 5-deacetylated analogue of **10** underwent bromination at C-6 and C-8 only).[14] A direct Suzuki coupling with **12** was attempted [with an excess K_2CO_3 (6.2 equiv) because of 5, 7, 3′ free phenol groups], which provided the expected compound **26** under tedious conditions of isolation because of the polar character of 7-hydroxyflavones. Therefore, we thought that **26** would be more conveniently obtained by carrying out the Suzuki coupling from a lipophilic 3-bromodiosmetin protected at the 7-OH group, such as the 7-isopropyl or 7-benzyl ethers **13** and **14**. As expected, **13** and **14** led easily and in good yields (69 and 73%) to the corresponding coupling compounds **27** and **25**. However, we observed that the removal of the isopropyl group of **27** by BCl_3 in CH_2Cl_2 always competed, more or less according to temperature, with demethylation of the 4″-methoxy group (at 0 °C, the 4″-*O*-demethyl **29** was even the sole reaction compound starting from **25** or **27**). In contrast, removal of the benzyl group by hydrogenolysis over Pd–C afforded quantitatively **26** from **25**. In order to study the influence of the substitution at C-5 on bioactivity, the two methyl ethers **24** and **28** were also synthesized. Access to **24** and **28** made use of the known weaker reactivity of the 5-OH towards alkylation (by involvement into chelation with the carbonyl) and the observed slower hydrogenolysis of the 3′benzyl ether group (probably by steric hindrance).

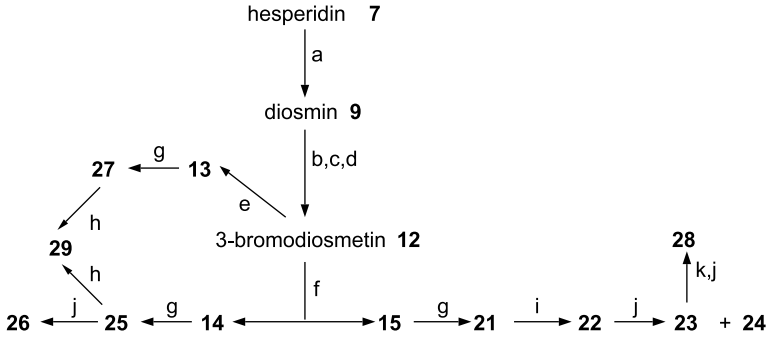
2.1.2. Analogues of combretastatin 2.

Three analogs of deoxy CA-4 **2** were prepared, semisynthetically (**30** and **31**) and by total synthesis (**32**). Access to **30** and **31** was performed from linarin **16**, a natural flavonoid previously obtained in our laboratory by deoxygenation of diosmin.[15] Synthesis of **30** and **31** from **16** via 3-bromoacacetin **17** and 7-benzyl-3-bromoacacetin **18** was similar to the sequence **9**→**12**→**14**→**25**→**26** depicted in Scheme 1. Compound **32**, unsubstituted at C-5 and C-7, was obtained from the commercial (2-hydroxybenzoyl)methylenetriphenylphosphorane **35** by a four-step sequence via the flavones **19**

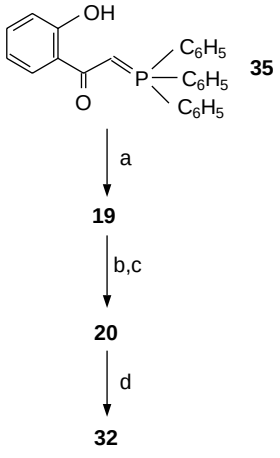




R_1	R_2	R_3	R_4		R_1	R_2	R_3	R_4	
				Analogues of combretastatin **1**					
O-Rutinosyl	OH	H	OH	**9**	OBn	OBn	Me	OH	**21**
O-HAR*	OAc	H	OAc	**10**	OBn	OBn	Me	OMe	**22**
O-HAR	OAc	Br	OAc	**11**	OH	OBn	Me	OMe	**23**
OH	OH	Br	OH	**12**	OH	OH	Me	OMe	**24**
O-Isopropyl	OH	Br	OH	**13**	OBn	OH	Me	OH	**25**
OBn	OH	Br	OH	**14**	OH	OH	Me	OH	**26**
OBn	OBn	Br	OH	**15**	O-Isopropyl	OH	Me	OH	**27**
					OMe	OH	Me	OMe	**28**
* Hexaacetylrutinosyl					OH	OH	H	OH	**29**
				Analogues of combretastatin **2**					
O-Rutinosyl	H	H	OH	**16**	OBn	H	Me	OH	**30**
OH	H	Br	OH	**17**	OH	H	Me	OH	**31**
OBn	H	Br	OH	**18**	H	H	Me	H	**32**
H	H	H	H	**19**					
H	H	Br	H	**20**					



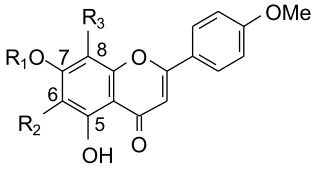
Scheme 1. Reagents and conditions: (a) I_2, pyridine, 90 °C, 16 h, 90%; (b) Ac_2O, pyridine, rt, 72 h, 95%; (c) NBS, CH_2Cl_2/pyridine 4:1, rt, 20 h, 90%; (d) HCl 11 N, 50 °C, 2 h, 75%; (e) 2-bromopropane, K_2CO_3, DMF, 75 °C, 6 h, 54%; (f) benzyl chloride, $KHCO_3$, DMF, 120 °C, 2.5 h, 34% (**14**), 34% (**15**); (g) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, reaction time-yield: 3 h-95% (**21**), 3 h-73% (**25**), 4 h-69% (**27**); (h) BCl_3, CH_2Cl_2, −78 °C 30 min, then 0 °C 15 h, 43% (from **25**); (i) $(CH_3)_2SO_4$, tetrabutylammonium hydrogen sulfate, CH_2Cl_2–NaOH 0.5 N, rt, 22 h 65%; (j) H_2, Pd–C 10%, DMF, rt, reaction time-yield: 72 h-45% (**23**) and 10% (**24**), 3 h-96% (**26**), 5 days after; (k) 39% (**28** from **23**); (l) iodomethane, K_2CO_3, DMF, rt, 20 h.



Scheme 2. Reagents and conditions: (a) 4-methoxybenzoyle chloride, pyridine, toluene, reflux, 5 h (65%); (b) NBS, CH_2Cl_2/MeOH 2:1, rt, 3 h; (c) THF/NaOH N 1:3, rt, 3 h, 42% (**20** from **19**); (d) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, 4 h-42%.

and **20** according to Le Corre[16] for synthesis of **19** and Brown[17] for bromination to **20** (Scheme 2).

2.1.3. Analogues of combretastatin 3. An easy semisynthetic entry to **47** and **48**, two analogues of aminocombretastatin **3**, requires a regiospecific nitration at C-3′. First attempts were undertaken with acacetin **36**, easily available from linarin **16**. Prior deactivation of C-6 and C-8 positions towards nitration seemed necessary and was accomplished by esterification of the 7-OH phenol group as benzylsulfonate. This group, recently described as a valuable protecting and deactivating group in phenol chemistry, is stable under many drastic conditions and easily removed by catalytic hydrogenolysis.[18] Unfortunately, nitration of 7-*O*-benzylsulfonate **37** (HNO_3 1 equiv in TFA, 0 °C, 2 h) provided the mixture (4/3) of 6 and 8-nitro compounds **38** and **39** (68%). Under the same conditions, the more deactivated 5,7-disulfonate led to a mixture with the starting compound still major after 24 h.

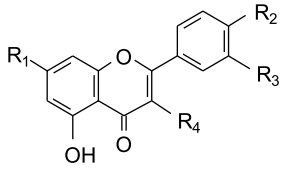


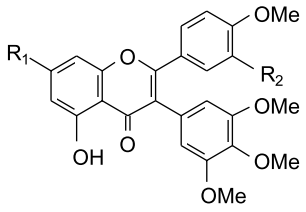
R_1	R_2	R_3	
H	H	H	**36**
$C_6H_5CH_2SO_2$	H	H	**37**
$C_6H_5CH_2SO_2$	NO_2	H	**38**
$C_6H_5CH_2SO_2$	H	NO_2	**39**

These negative results led us to select, as starting material, a 4′-hydroxyflavone with a C-3′ position more activated towards nitration than in acacetin derivatives (Scheme 3). The *Citrus* flavanone naringin **8** provided this 4′-hydroxyflavone, rhoifolin **40**, by the same dehydrogenation procedure (I_2–pyridine) previously described to obtain diosmin. The key nitration step of rhoifolin **40** into 3′-nitrorhoifolin **41** was accomplished very easily by 1 equiv HNO_3 in TFA at 0 °C. The choice of TFA as solvent on the one hand, a strict stoichiometry of HNO_3 on the other hand, prevented **40** from any hydrolysis of glycosidic bonds. It is noteworthy that presence of the sugar moiety at C-7 makes the nitration of the flavone at C-3′ very clean: under the same conditions applied to apigenin (5,7,4′-trihydroxyflavone), significant nitration was also observed at the other benzene ring.[19] A direct hydrolysis of crude **41** gave 3′-nitroapigenin **42** while a prior methylation then acid hydrolysis furnished 3′-nitroacacetin **43**. This compound led by a similar sequence (acetylation, bromination, hydrolysis, alkylation, Suzuki coupling) as described in the 3′ hydroxy series to the nitro products **33** and **34**. A last step of catalytic hydrogenation (Pd–C, rt) gave, respectively, the expected analogues **47** and **48** by reduction of the nitro group and, in the case of **34**, concomitant debenzylation of the ether group.

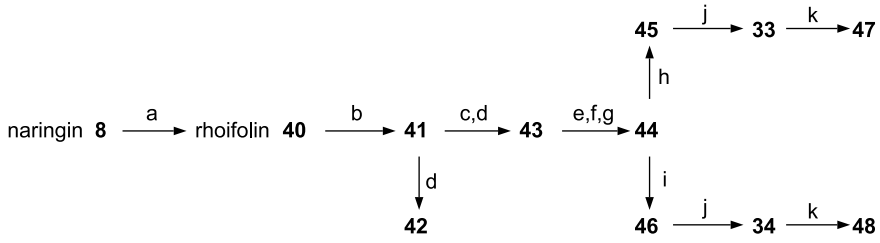
2.2. Synthesis of analogues of the group B (54, 58 and 59)

In order to study a possible influence on the bioactivity, we then synthesized compounds displaying a reverse relative position of the two phenyl rings of the combretastatin moiety on the chromone. Lack of easily available natural flavones with a trimethoxyphenyl ring at C-2 made total synthesis necessary. Three compounds, **54**, **58** and **59**, isomers, respectively, of **32**, **31** and **26** were prepared.

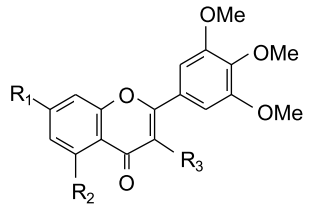




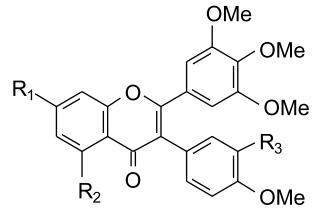
R_1	R_2	R_3	R_4		R_1	R_2	
Analogues of combretastatin **3**							
O-Neohesperidosyl	OH	H	H	**40**	OMe	NO_2	**33**
O-Neohesperidosyl	OH	NO_2	H	**41**	OBn	NO_2	**34**
OH	OH	NO_2	H	**42**	OMe	NH_2	**47**
OH	OMe	NO_2	H	**43**	OH	NH_2	**48**
OH	OMe	NO_2	Br	**44**			
OMe	OMe	NO_2	Br	**45**			
OBn	OMe	NO_2	Br	**46**			



Scheme 3. Reagents and conditions: (a) I_2, pyridine, 90 °C, 16 h, 95%; (b) HNO_3 53%, TFA, 0 °C, 2 h, quantitative yield (crude **41**); (c) iodomethane, K_2CO_3, DMF, rt, 48 h; (d) HCl 11 N, 60 °C, 1 h, 73% (**43** from **41**), 83% (**42**); (e) Ac_2O, pyridine, rt, 72 h, 95%; (f) NBS, CH_2Cl_2/MeOH 2:1, rt, 3 h, 86%; (g) THF/NaOH N 1:1, rt, 4 h, 80%; (h) iodomethane, K_2CO_3, DMF, rt, 20 h, quantitative yield; (i) benzyl chloride, $KHCO_3$, DMF, 120 °C, 2 h, 86%; (j) 3,4,5-trimethoxybenzeneboronic acid, $Pd(PPh_3)_4$, K_2CO_3 2 N, dioxane, reflux, reaction time-yield: 3 h-77% (**33**), 2.5 h-84% (**34**); (k) H_2, Pd–C 10%, DMF, rt, 3 h, quantitative yield (**47** and **48**).



R_1	R_2	R_3	
H	H	H	**49**
H	H	Br	**50**
OH	OH	H	**51**
OH	OH	Br	**52**
OBn	OH	Br	**53**
OBn	OH	H	**57**

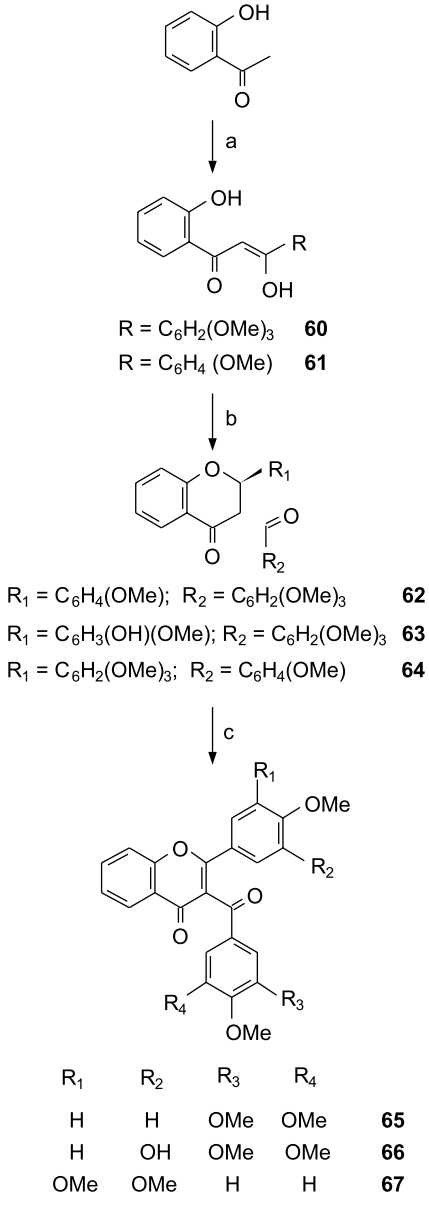


R_1	R_2	R_3	
H	H	H	**54**
OBn	OH	H	**55**
OBn	OH	OBn	**56**
OH	OH	H	**58**
OH	OH	OH	**59**

Synthesis of **54** via 3′,4′,5′-trimethoxyflavone **49** and its 3-bromoderivative **50** followed the procedure described for **32**. However, the Suzuki coupling step between **50** and 4-methoxyphenylboronic acid led to **54** with a poor yield (13%) because of a major debromination of **50** into **49**. This unwanted reaction was proved to be related to the boronic acid, since the same result was observed by coupling 7-benzyl-3-bromodiosmetin **14** with 4-methoxyphenylboronic acid (vs 73% yield between **14** and trimethoxyphenylboronic acid, vide supra). Therefore we turned to another method for this last step by using a iron-catalysed Grignard coupling developed in the laboratory.[20] The cross-coupling reaction of 4-methoxyphenylmagnesium bromide with **50** [THF, −25 °C, $Fe(acac)_3$] again provided a mixture **54/49** but **54** was isolated with a slightly more favourable yield (18%). Preparation of the 5,7-dihydroxylated analogues **58** and **59** started with synthesis of the 5,7-dihydroxy-3′,4′,5′-trimethoxyflavone (=tricetin trimethyl ether) **51** from (2,4,6-trihydroxybenzoyl)methylenetriphenylphosphorane,[21] and proceeded through the 3-bromo derivative **52** and its 7-benzyl ether **53** as already described in the **A** group. The coupling step of **53** at C-3 was then carried out by both methods: Suzuki reaction with commercial 4-methoxyphenylboronic acid produced the expected **55** (21%), while iron-catalysed Grignard coupling with 3-benzyloxy-4-methoxyphenylmagnesium bromide[22] led to **56** (12%). A major debromination reaction into **57** again accounts for low yields of both couplings. Lastly, catalytic hydrogenolysis (Pd–C, rt) of **55** and **56** gave the expected analogues **58** and **59** quantitatively.

2.3. Synthesis of analogues of the groups C (65, 66) and D (67)

Taking into account the positive effect observed in some bicyclic analogues of combretastatins by addition of a C=O linker,[9,10] we synthesized three 3-aroylflavones bearing at C-3 either a 3,4,5-trimethoxyphenyl ring (**65**, **66**) or a 4-methoxyphenyl ring (**67**). First attempts to prepare such compounds from 3-bromoflavones by use of BuLi and the adequate aroyl chloride were unsuccessful so that we turned to classical synthesis of 3-aroylflavones.[23] Starting from 2′-hydroxyacetophenone and 3,4,5-trimethoxy or 4-methoxybenzoyl chlorides, access to **65**–**67** (Scheme 4) proceeded in three steps: (a) one-pot esterification of the phenol group followed by a Baker–Vankataraman rearrangement into **60**



Scheme 4. (a) 3,4,5-Trimethoxybenzoyle chloride or 4-methoxybenzoyle chloride, pyridine, 0 °C, 5 min, then rt, 2.5 h; addition of anhydrous KOH, 100 °C, 3 h, 37% (**60**) and 34% (**61**); (b) *p*-anisaldehyde or isovanillin or 3,4,5-trimethoxybenzaldehyde, piperidine, EtOH, reflux, reaction time: 5 h; (c) SeO_2, dioxane, reflux, 6 h, 36% (**65** from **60**), 40% (**66** from **60**), 54% (**67** from **61**).

and **61** [according to ^{1}H NMR spectra, **61** was the pure keto-enol, while **60** was a mixture of β-diketone (18%) and keto-enol (82%) forms]; (b) Knoevenagel condensation of **60** with *p*-anisaldehyde or isovanillin, and of **61** with 3,4,5-trimethoxybenzaldehyde giving, respectively, crude 3-aroylflavanones **62**, **63** and **64**, which were used in the next step without purification [formation of the trans aroylflavanone form as a major compound was proved in ^{1}H NMR by the presence of H-2 and H-3 signals (2d, $J=12.8$ Hz about 5.0 and 5.8 ppm)]; (c) dehydrogenation of **62**, **63**, **64** by SeO_2 into the desired 3-aroylflavones **65**, **66** and **67**.

2.4. Biological activity

Inhibition of tubulin polymerization (ITP) was determined according to Zavala and Guenard's method.[24] Compounds were tested at 0.1 mg/mL ($\approx 2\times10^{-4}$ M) and estimated inactive when they decreased by less than 30% the maximum assembly rate of tubulin without drug. The IC_{50} was calculated only for the most active compounds and expressed in relation to colchicine in terms of the $IC_{50}/IC_{50\ colchicine}$ ratio. As depicted in Table 1, results were disappointing since only seven of the twenty tested compounds displayed an activity, usually in a medium range. Compound **31**, with a substructure of deoxycombretastatin A4 **2**, was the most active, while all the other 5,7-dioxygenated synthesized analogues, having combretastatin A4 **1** (**24**–**28** and **59**) or aminocombretastatin **3** (**47**, **48**) substructures, were devoid of activity. It is worth noting about analogues of **2** that inversion of substituents at C2 and C3 interfered strongly with activity in one case (**31** vs **58**) but was almost ineffective (**32** vs **54**) in another one. Lastly, insertion of a C=O linker between C3 and the phenyl ring seemed favourable to ITP (**65** vs **32** and, to a lower extent, **67** vs **54**) with, once again, a better activity with the analogue of **2** (**65** vs **66**).

Table 1. ITP activity

Compound	Activity [a]
Analogs of **1**	
24	Inactive [b]
25	Inactive
26	Inactive
27	Inactive
28	Inactive
59	Inactive
Analogs of **2**	
30	Inactive [b]
31	2.4[c]
32	40%[d]
54	54%
55	35%
58	Inactive
Analogs of **3**	
47	Inactive
48	Inactive
Other 3-arylflavones	
29	Inactive
33	Inactive
34	Inactive
3-Aroylflavones	
65	5.4[c]
66	39%
67	66%
Reference	
Colchicine	1

[a] Measurement at 0.1 mg/mL.
[b] Decreasing $<30\%$.
[c] $IC_{50}/IC_{50colchicine}$.
[d] Decreasing of the maximum assembly rate of tubulin without drug.

3. Conclusion

Though failing in its initial goal of access to new combretastatins analogues with strong ITP activity, this study seems to us noteworthy from a chemical point of view for the following reasons: (a) access to 3-phenyl flavones via a cross-coupling reaction from 3-bromo-5,7-dioxygenated flavones led us to achieve a very easy and regiospecific 3-bromination of natural 5,7-dihydroxyflavones and their 7-glycosides (3-bromination of synthetic flavones is well documented,[17,25] but has never been described to the best of our knowledge from natural 5,7-dihydroxyflavones); (b) the C3-aryl bond was usually formed via a Suzuki reaction, but the coupling with a Grignard reagent, easier to prepare than a boronic acid, seemed to be a possible alternative; (c) synthesis of analogues of aminocombretastatin **3** allowed us to develop an original nitration process of a flavone glycoside without prior protection nor hydrolysis of the sugar moiety; (d) lastly, most of this study started from two easily available *Citrus* flavonoids, hesperidin and naringin, which confirms the interest of some natural products as raw materials for organic chemistry.

4. Experimental

4.1. General experimental procedures

Melting points were determined with a micro-Koffler and are uncorrected. ^{1}H NMR spectra were recorded on Bruker AC-200 (200 MHz) or Bruker AM-400; NOESY experiments and the ^{1}H–^{1}H (COSY) and ^{1}H–^{13}C (HMQC and HMBC) were performed with a Bruker AM-400. EIMS were registered on an Automass Thermoquest with EI source (70 eV) and ESIMS on a Navigator Aqa thermoquest with an ES source (MeOH, flow rate: 5 μL/min) (70 eV). MHz spectrometers. Flash chromatography (FC) was performed with silica gel 60 (9385 Merck) or aluminium oxide 90 (1097 Merck), or alumina 90 standard II–III (1097 Merck). Preparative TLC were performed with 60 F 254 silica gel (5715 Merck) or 60 F 254 aluminium oxide (5713 Merck).

4.2. Synthesis of analogues of the group A

4.2.1. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 1 and 2.

4.2.1.1. 3-Bromo-octoacetyldiosmin 11. A solution of diosmin **9** (3.04 g, 5 mmol) in Ac_2O/pyridine 1:5 (20 mL) was left at rt for 48 h. The reaction mixture was taken up in iced water, stirred at 0 °C for 2 h then extracted with CH_2Cl_2. Standard work-up of the organic layer provided an amorphous residue of pure octoacetyldiosmin **10** (4.5 g, 95%). A solution of **10** (4.25 g, 4.5 mmol) in CH_2Cl_2/pyridine 5:1 (50 mL) was added with NBS (4.05 g, 22.5 mmol) then kept at rt for 20 h. The reaction mixture was taken up in CH_2Cl_2, washed with water and evaporated to dryness. The dried residue was left at rt for 20 h more

(this step allowed completion of the bromination), then taken up in CH_2Cl_2, and washed with 0.1 M aqueous sodium thiosulphate then water. Standard work-up of the reaction, then purification of the residue by FC (silica gel, CH_2Cl_2/MeOH 98.5:1.5) led to 3-bromo-octoacetyldiosmin **11** (4.15 g, 90%). Yellowish amorphous powder. ^{1}H NMR ($CDCl_3$) δ [aglycone moiety]: 2.33 and 2.44 (6H, 2s, OAc-5 and 3′), 3.91 (3H, s, OMe-4′), 6.69 (1H, d, J=2 Hz, H-6), 6.89 (1H, d, J=2 Hz, H-8), 7.08 (1H, d, J=8.8 Hz, H-5′), 7.58 (1H, d, J=2.2 Hz, H-2′), 7.77 (1H, dd, J=8.8, 2.2 Hz, H-6′); [sugar moiety: inner glucose (″) and terminal rhamnose (‴)] 1.13 (3H, d, J=6.4 Hz, H-6‴), 1.92–2.06 (18H, 6s, 6 sugar acetyles). 3.66 (1H, H-6″), 3.80 (2H, H-6″ and H-5‴), 3.94 (1H, H-5″), 4.67 (1H, s, H-1‴), 4.99 (1H, H-4‴), 5.13–5.28 (5H, H-2″, 3″, 4″, 2‴ and 3‴), 5.27 (1H, H-1″). ^{13}C NMR ($CDCl_3$) δ [aglycone moiety] 56.0 (OMe-4′), 101.4 (C-8), 109.5 and 110.7 (C-3 and C-10), 109.8 (C-6), 111.6 (C-5′), 124.1 (C-2′), 124.5 (C-1′), 128.7 (C-6′), 139.2 (C-3′), 150.8 (C-5), 153.4 (C-4′), 157.6 (C-9), 159.7 and 159.9 (C-2 and C-7), C-4 not detected; [sugar moiety: inner glucose (″) and terminal rhamnose (‴)] 17.2 (C-6‴), 65.9 (C-6″), 66.6 (C-5‴), 68.5, 68.8, 69.1, 70.6, 70.7 and 72.2 (C-2″, C-3″, C-4″, C-2‴, C-3‴ and C-4‴), 73.5 (C-5″), 97.5 (C-1″), 97.9 (C-1‴); 20.5–21 and 168.6–170.6 (8 sugar acetyl groups).

4.2.1.2. 3-Bromodiosmetin 12. 3-Bromo-octoacetyldiosmin **11** (4 g, 3.9 mmol) in aqueous 11 N HCl (75 mL) was stirred at 55 °C for 2 h and left for 2 h at rt. The resulting suspension was filtered, washed several times with water then dried with P_2O_5 under vacuum to yield a crude residue of 3-bromodiosmetin **12**, which was crystallized from MeOH (1.11 g, 75%). Beige-yellowish crystals: mp> 300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.87 (s, 3H, OMe-4′), 6.27 (d, J=1.8 Hz, 1H, H-6), 6.40 (d, J=1.8 Hz, 1H, H-8), 7.09 (d, J=8.2 Hz, 1H, H-5′), 7.31 (d, J=2 Hz, 1H, H-2′), 7.33 (dd, J=8.2, 2 Hz, 1H, H-6′), 9.46 (s, 1H, OH-3′), 11.0 (s, 1H, OH-7), 12.38 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.1 (OMe-4′), 94.2 (C-8), 99.6 (C-6), 102.9 (C-10), 105.1 (C-3), 111.9 (C-5′), 116.5 (C-2′), 121.8 (C-6′), 124.5 (C-1′), 146.4 (C-3′), 150.7 (C-4′), 157.2 (C-9), 161.2 and 162.3 (C-2 or C-5), 165.0 (C-7), 176.7 (C-4). EIMS m/z (%) 380–378 (M^+, 92–100), 379–377 (54–38).

4.2.1.3. 3-Bromodiosmetin 7-isopropyl ether 13. To a mixture of **12** (152 mg, 0.4 mmol) and K_2CO_3 (55 mg, 0.4 mmol) in DMF (6 mL) was added isopropyl bromide (0.4 mL, 4 mmol) and the mixture stirred under nitrogen for 6 h at 75 °C. The reaction mixture was cooled, filtered, and evaporated to dryness. The dried residue was purified by FC (silica gel, CH_2CH_2/MeOH 99.5:0.5) to provide 3-bromodiosmetin 7-isopropyl ether **13** (90 mg, 54%). Pale-yellow crystals: mp: 182–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.37 (d, J=6 Hz, 6H, isopropyl), 4.62 (heptuplet, J=6 Hz, 1H, isopropyl), 3.99 (s, 3H, OMe-4′), 6.38 and 6.39 (2d, J= 2 Hz, 2H, H-6 and H-8), 6.97 (d, J=8.4 Hz, 1H, H-5′), 7.44 (d, J=2.1 Hz, 1H, H-2′), 7.46 (dd, J=8.4, 2.1 Hz, 1H, H-6′), 12.36 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 21.7 (isopropyl), 55.9 (OMe-4′), 71.0 (isopropyl), 93.2 (C-8), 99.6 (C-6), 103.8 (C-10), 110.0 (C-5′), 115.4 (C-2′), 121.9 (C-6′), 125.4 (C-1′), 145.5 (C-3′), 149.1 (C-4′), 156.9 (C-9), 161.2 (C-2), 162.0 (C-5), 164.1 (C-7); C-3 and C-4 not detected.

4.2.1.4. 3-Bromodiosmetin 7-benzyl ether 14 and 3-bromodiosmetin 7,3′-dibenzyl ether 15. To a mixture of **12** (380 mg, 1 mmol) and $KHCO_3$ (150 mg, 1.5 mmol) in DMF (10 mL) was added benzyl chloride (0.23 mL, 2 mmol) and the mixture stirred under nitrogen for 2.5 h at 120 °C. The reaction mixture was cooled, filtered, and evaporated to dryness. The dried residue was purified by FC (silica gel, CH_2CH_2 then CH_2CH_2/MeOH 99:1) to provide 3-bromodiosmetin 7,3′-dibenzyl ether **15** (190 mg, 34%) then 3-bromodiosmetin 7-benzyl ether **14** (160 mg, 54%). Compound **14**. Pale-yellow crystals: mp: 191–194 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′), 5.25 (s, 2H, benzyl), 6.57 (d, J=2 Hz, 1H, H-6), 6.80 (d, J= 2 Hz, 1H, H-8), 7.12 (d, J=8.4 Hz, 1H, H-5′), 7.3–7.5 (m, 7H, H-2′, H-6′ and benzyl), 9.50 (s, 1H, OH-3′), 12.40 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.1 (OMe-4′), 70.5 (benzyl), 93.7 (C-8), 99.4 (C-6), 103.9 (C-10), 105.4 (C-3), 111.9 (C-5′), 116.6 (C-2′), 121.9 (C-6′), 124.4 (C-1′), 128.2, 128.5 and 128.9 (benzyl), 136.3 (benzyl), 146.4 (C-3′), 150.8 (C-4′), 157.1 (C-9), 160.9 (C-5), 162.8 (C-2), 164.9 (C-7), 176.9 (C-4). Compound **15**. Yellow crystals: mp: 165–167 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.98 (s, 3H, OMe-4′), 5.11 and 5.23 (2s, 4H, benzyls), 6.45 and 6.47 (2d, J=2 Hz, 2H, H-6 and H-8), 7.00 (d, J=8.4 Hz, 1H, H-5′), 7.3–7.5 (m, 12H, H-2′, H-6′ and benzyls), 9.50 (s, 1H, OH-3′), 12.40 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.0 (OMe-4′), 70.5 and 71.3 (benzyls), 93.1 (C-8), 99.2 (C-6), 104.2 (C-10), 105.7 (C-3), 111.0 (C-5′), 115.4 (C-2′), 123.5 (C-6′), 124.3 (C-1′), 127.1, 127.3, 127.4, 128.0, 128.3 and 128.7 (benzyls), 135.5 and 136.3 (benzyls), 147.4 (C-3′), 152.3 (C-4′), 157.0 (C-9), 161.7 (C-2 and C-5), 164.8 (C-7), 177.0 (C-4).

4.2.1.5. 3-Bromoacacetin 17; 3-bromoacacetin 7-benzyl ether 18. 3-Bromoacacetin **17** was prepared from 900 mg (1.5 mmol) linarin **16** as **12** from **9** (60% **17** from **16**), then its benzyl ether **18** as **14** from **12** (1.1 equiv $KHCO_3$, 1.2 equiv BnCl, 77%). Compound **17**. Beige-yellowish crystals: mp: 297–298 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.86 (s, 3H, OMe-4′), 6.27 (d, J=2 Hz, 1H, H-6), 6.41 (d, J=2 Hz, 1H, H-8), 7.12 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.84 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 11.0 (s, 1H, OH-7), 12.37 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 94.3 (C-8), 99.7 (C-6), 102.9 (C-10), 105.2 (C-3), 114.2 (C-3′ and C-5′), 124.4 (C-1′), 131.6 (C-2′ and C-6′), 157.2 (C-9), 161.2, 161.9 and 162.0 (C-2, C-5 and C-4′), 165.0 (C-7), 176.7 (C-4). ESIMS (+) m/z 387–385 $[M+Na]^+$, 365–363 $[M+H]^+$. Compound **18**. Light-yellow crystals: mp: 134–136 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′), 5.13 (s, 2H, benzyl), 6.50 (s, 2H, H-6 and H-8), 7.02 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 7.87 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.41 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe-4′), 70.6 (benzyl), 93.2 (C-8), 99.3 (C-6), 104.1 (C-10), 105.6 (C-3), 113.7 (C-3′ and C-5′), 124.4 (C-1′), 127.4, 128.4 and 128.7 (benzyl), 131.2 (C-2′ and C-6′), 135.6 (benzyl), 157.1 (C-9), 161.7, 161.8 and 162.0 (C-2, C-5 and C-4′), 164.9 (C-7), 177.0 (C-4).

4.2.1.6. 4′-Methoxyflavone 19. Flavone **19** (655 mg, 65% from 4 mmol phosphorane) was prepared according to Ref.16 White-yellowish crystals: mp: 159–161 °C (MeOH), lit.[16] 157–158 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OMe-4′),

6.75 (s, 1H, H-3), 7.03 (d, $J=9$ Hz, 2H, H-3′ and H-5′), 7.41 (t, $J=8.1$ Hz, 1H, H-6), 7.55 (dd, $J=7.8$, 1.4 Hz, 1H, H-8), 7.69 (m, 1H, H-7), 7.90 (d, $J=9$ Hz, 2H, H-2′ and H-6′), 8.23 (dd, $J=8.1$, 1.7 Hz, 1H, H-5).

4.2.1.7. 3-Bromo-4′-methoxyflavone 20. Bromination of the flavone **19** was performed from Ref. 17: a solution of **19** (504 mg, 2 mmol) in CH_2Cl_2/MeOH 2:1 (60 mL) was added with NBS (712 mg, 4 mmol) then kept at rt for 3 h. The reaction mixture was taken up in CH_2Cl_2, and washed with 0.1 M aqueous sodium thiosulphate then water. Standard work-up furnished a dried residue, which was dissolved then stirred in the mixture THF/NaOH 0.5 M 1:3 (60 mL) for 3 h at rt. The reaction mixture was adjusted to pH 6 with HCl 11 N then extracted with CH_2Cl_2. Standard work-up of the reaction, then purification of the residue by FC (alumina, CH_2Cl_2) led to 3-bromo-4′-methoxyflavone **20** (276 mg, 42%). **20**. Light-yellow crystals: mp: 137–139 °C (MeOH), lit.[25d] 140–141 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H, OMe-4′), 7.04 (d, $J=8.9$ Hz, 2H, H-3′ and H-5′), 7.40–7.55 (m, 2H, H-6 and H-8), 7.65–7.75 (m, 1H, H-7), 7.88 (d, $J=8.9$ Hz, 2H, H-2′ and H-6′), 8.29 (dd, $J=7.9$, 1.5 Hz, 1H, H-5).

4.2.2. Synthesis of 3-arylflavones analogues of 1 and 2. Typical procedure of the Suzuki cross-coupling reaction: a 3-bromoflavone (0.1 mmol), 3,4,5-trimethoxybenzeneboronic acid (35 mg, 0.16 mmol) and tetrakis(triphenylphosphine)palladium (5 mg, 0.005 mmol) were added in a flask fitted with a reflux condenser. The flask was evacuated and back-filled with nitrogen and then 3 mL of dioxane and 0.16 mL of a 2 M solution of K_2CO_3 were added (with 3-bromo-hydroxyflavones, 0.05 mL 2 M K_2CO_3 more were added per each phenol group). The reaction mixture was stirred at 110 °C until completion of the reaction. After cooling, the mixture was taken up in water, adjusted to pH 6 with 1 N HCl and extracted with CH_2Cl_2. Standard work-up then purification by FC led to the expected 3-arylflavone.

4.2.2.1. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7,3′-dibenzyl ether 21. Prepared by Suzuki cross-coupling from 224 mg (0.4 mmol) **15**; yield 95% (245 mg). Light-yellow crystals: mp: 182–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 6H, OMe-3″ and 5″), 3.84 (s, 3H, OMe-4″), 3.87 (s, 3H, OMe-4′), 4.86 (s, 2H, benzyl-3′), 5.17 (s, 2H, benzyl-7), 6.46 (s, 2H, H-2″ and H-6″), 6.46 and 6.49 (2d, $J=2$ Hz, 2H, H-6 and H-8), 6.79 (d, $J=8.5$ Hz, 1H, H-5′), 6.89 (d, $J=2.1$ Hz, 1H, H-2′), 7.11 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.2–7.5 (m, 10H, benzyls), 12.87 (s, 1H, OH-5). EIMS *m/z* (%) 646 (M^+, 73), 556 (76), 555 (100), 540 (47).

4.2.2.2. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7,3′-dibenzyl-5-methyl ether 22. A solution of **21** (183 mg, 0.28 mmol) in CH_2Cl_2 (30 mL) was stirred for 22 h at rt in the presence of 0.5 M aqueous NaOH (30 mL), dimethyl sulfate (3 mL) and tetrabutylammonium hydrogen sulfate (50 mg) as phase-transfer catalyst. Standard work-up of the organic layer, then purification of the dry residue by FC (silica gel, CH_2Cl_2/MeOH 99:1; alumina, CH_2Cl_2/MeOH 99.5:0.5) provided **22** (121 mg, 65%). Pale-yellow crystals: mp: 163–166 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 6H, OMe-3″ and 5″), 3.84 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 3.92 (s, 3H, OMe-5), 4.85 (s, 2H, benzyl-3′), 5.18 (s, 2H, benzyl-7), 6.45 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=1.8$ Hz, 1H, H-6), 6.56 (d, $J=1.8$ Hz, 1H, H-8), 6.80 (d, $J=8.5$ Hz, 1H, H-5′), 6.90 (d, $J=2.1$ Hz, 1H, H-2′), 7.12 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.2–7.5 (m, 10H, benzyls). ^{13}C NMR ($CDCl_3$) δ 55.8 (CH_3, OMe-4′), 55.9 ($2CH_3$, OMe-3″ and 5″), 56.1 (OMe-5), 60.8 (OMe-4″), 70.2 (benzyl-7), 70.4 (benzyl-3′), 93.0 (C-8), 96.2 (C-6), 108.1 (C-2″ and C-6″), 108.7 (C-10), 110.7 (C-5′), 114.1 (C-2′), 122.1 (C-3), 122.5 (C-6′), 124.9 (C-1′), 126–130 (benzyls), 128.3 (C-1″), 135.5 (C, benzyl-7), 136.1 (benzyl-3′), 137.0 (C-4″), 147.0 (C-3′), 151.0 (C-4′), 152.7 (C-3″ and C-5″), 157.8 (C-2), 158.9 (C-9), 161.1 (C-5), 162.9 (C-7); C-4 not detected. EIMS *m/z* (%) 660 (M^+, 11), 570 (43), 569 (100), 541 (28).

4.2.2.3. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 3′-benzyl-5-methyl ether 23 and 3-(3″,4″,5″-trimethoxyphenyl)diosmetin 5-methyl ether 24. A solution of **22** (86 mg, 0.13 mmol) in DMF (3 mL) was hydrogenated under 1 atm pressure hydrogen with 10% Pd–C (8.5 mg) at rt for 72 h. The catalyst was separated and the filtrate concentrated to dryness. Crystallization of the dried residue from CH_2Cl_2–MeOH afforded pure **23** (26 mg, 35%), while TLC (silica gel, CH_2Cl_2/MeOH 94:6) of the mother liquor provided **23** (8 mg, 10%) and **24** (6 mg, 10%). Compound **23**. Pale-yellow crystals: mp: 206–210 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 9H, OMe-3″, 4″ and 5″), 3.74 (s, 3H, OMe-4″), 3.78 (s, 3H, OMe-4′), 3.92 (s, 3H, OMe-5), 4.70 (s, 2H, benzyl), 6.38 (d, $J=1.8$ Hz, 1H, H-6), 6.43 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=1.8$ Hz, 1H, H-8), 6.93 (d, $J=8.5$ Hz, 1H, H-5′), 6.97 (d, $J=1.7$ Hz, 1H, H-2′), 7.13 (dd, $J=8.5$, 1.7 Hz, 1H, H-6′), 7.3–7.4 (m, 5H, benzyl groups). HRESIMS *m/z* 593.1818 (calcd for $C_{33}H_{30}O_9Na$, 593.1788). Compound **24**. Pale-yellow crystals: mp: 267–270 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 3.78 (s, 3H, OMe-5), 6.38 (d, $J=2$ Hz, 1H, H-6), 6.40 (s, 2H, H-2″ and H-6″), 6.43 (d, $J=2$ Hz, 1H, H-8), 6.78 (dd, $J=8.2$, 1.9 Hz, 1H, H-6′), 6.85 (d, $J=8.2$ Hz, 1H, H-5′), 6.86 (d, $J=1.9$ Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6) δ 55.6 (OMe-7, 4′, 3″ and 5″), 59.8 (OMe-4″), 94.4 (C-8), 96.6 (C-6), 109.0 (C-2″ and C-6″), 111.1 (C-5′), 115.7 (C-2′), 121.1 (C-6′), 121.8 (C-3), 124.4 (C-1′), 136.4 (C-4″), 145.5 (C-3′), 148.8 (C-4′), 151.8 (C-3″ and C-5″), 160.8 (C-5); C-2, C-4, C-7, C-9, C-10 and C-1″ not detected. HRESIMS *m/z* 503.1345 (calcd for $C_{26}H_{24}O_9Na$, 503.1318), 481.1543 (calcd for $C_{26}H_{25}O_9$, 481.1499).

4.2.2.4. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7-benzyl ether 25. Prepared by Suzuki cross-coupling from 282 mg (0.6 mmol) **14**; yield 73% (244 mg). Light-yellow crystals: mp: 235–238 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6H, OMe-3″ and 5″), 3.86 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 5.15 (s, 2H, benzyl-7), 6.45 (s, 2H, H-2″ and H-6″), 6.46 (d, $J=2.2$ Hz, 1H, H-6), 6.53 (d, $J=2.2$ Hz, 1H, H-8), 6.67 (d, $J=8.5$ Hz, 1H, H-5′), 6.79 (dd, $J=8.5$, 2.1 Hz, 1H, H-6′), 7.14 (d, $J=2.1$ Hz, 1H, H-2′), 7.3–7.5 (m, 5H, benzyl), 12.90 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.8 (OMe-4′), 55.9 (OMe-3″ and 5″), 60.7 (OMe-4″), 70.1 (benzyl), 92.7 (C-8), 98.3 (C-6), 105.4 (C-10), 107.8 (C-2″ and C-6″), 109.5 (C-5′), 115.0 (C-2′), 120.8 (C-3), 122.7 (C-6′), 125.3 (C-1′), 127–128.5 (benzyl), 127.2 (C-1″), 135.5 (benzyl), 137.1 (C-4″), 145.0 (C-3′), 147.5 (C-4′), 152.9 (C-3″ and C-5″), 157.0 (C-9), 161.8

(C-2), 162.1 (C-5), 164.3 (C-7); C-4 not detected. EIMS *m/z* (%) 556 (M^+, 45), 91 (100).

4.2.2.5. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 26. Catalytic hydrogenation of **25** (110 mg, 0.2 mmol) in DMF (Pd–C, rt, 3 h) provided after filtration of the catalyst a dry residue of pure **26** (87 mg, 96%). Pale-beige yellowish crystals: mp: 262–264 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 6.21 (d, J=2 Hz, 1H, H-6), 6.40 (d, J=2 Hz, 1H, H-8), 6.49 (s, 2H, H-2″ and H-6″), 6.83 (dd, J=8.5, 2 Hz, 1H, H-6′), 6.87 (d, J=8.5 Hz, 1H, H-5′), 6.90 (d, J=2 Hz, 1H, H-2′), 12.97 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.5 (OMe-4″), 93.3 (C-8), 99.0 (C-6), 103.2 (C-10), 108.5 (C-2″ and C-6″), 111.4 (C-5′), 116.1 (C-2′), 119.8 (C-3), 121.6 (C-6′), 124.9 (C-1′), 127.8 (C-1″), 137.1 (C-4″), 146.0 (C-3′), 149.8 (C-4′), 152.5 (C-3″ and C-5″), 157.2 (C-9), 161.9 (C-2), 162.0 (C-5), 164.2 (C-7); C-4 not detected. EIMS *m/z* (%) 466 (M^+, 100), 451 (48).

4.2.2.6. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 7-isopropyl ether 27. Prepared by Suzuki cross-coupling from 42 mg (0.1 mmol) **13**; purification by FC (silica gel, CH_2Cl_2/MeOH 98:2); yield 69% (35 mg). Light-yellow crystals: mp: 219–219 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J=6 Hz, 6H, isopropyl), 4.64 (heptuplet, J=6 Hz, 1H, isopropyl), 3.74 (s, 6H, OMe-3″ and 5″), 3.86 (s, 3H, OMe-4″), 3.89 (s, 3H, OMe-4′), 6.35 and 6.43 (2d, J=2.2 Hz, 2H, H-6 and H-8), 6.44 (s, 2H, H-2″ and H-6″), 6.68 (d, J=8.5 Hz, 1H, H-5′), 6.79 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 7.15 (d, J=2.1 Hz, 1H, H-2′), 12.86 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 21.6 (isopropyl), 55.8 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.6 (OMe-4″), 70.7 (isopropyl), 93.0 (C-8), 98.8 (C-6), 104.1 (C-10), 107.8 (C-2″ and C-6″), 110.0 (C-5′), 115.1 (C-2′), 120.8 (C-3), 122.7 (C-6′), 125.5 (C-1′), 137.0 (C-4″), 145.0 (C-3′), 147.9 (C-4′), 152.9 (C-3″ and C-5″), 157.1 (C-9), 162.2 (C-5); C-2, C-4, C-7 and C-1″ not detected. EIMS *m/z* (%) 508 (M^+, 100), 451 (33), 151 (27).

4.2.2.7. 3-(3″,4″,5″-Trimethoxyphenyl)diosmetin 5,7-dimethyl ether 28. Methylation of **23** (27 mg, 0.047 mmol) in DMF by the system K_2CO_3/MeI, then catalytic hydrogenation (DMF, rt, 5 days), and final purification by TLC (silica gel, CH_2Cl_2/MeOH 95:5) led to **28** (9 mg, 39% from **23**). Light-yellow crystals: mp: 178–180 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 6H, OMe-3″ and 5″), 3.85 (s, 3H, OMe-4″), 3.88 (s, 3H, OMe-4′), 3.91 (s, 3H, OMe-7), 3.93 (s, 3H, OMe-5), 6.38 (d, J=2.2 Hz, 1H, H-6), 6.46 (s, 2H, H-2″ and H-6″), 6.53 (d, J=2.2 Hz, 1H, H-8), 6.66 (d, J=8.5 Hz, 1H, H-5′), 6.77 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 7.19 (d, J=2.1 Hz, 1H, H-2′). ^{13}C NMR ($CDCl_3$) δ 55.7 and 56.3 (OMe-7 and 4′), 55.9 (2OMe-3″ and 5″), 60.9 (OMe-4″), 92.4 (C-8), 96.1 (C-6), 108.7 (C-10), 108.7 (C-2″ and C-6″), 109.8 (C-5′), 114.9 (C-2′), 122.5 (C-3), 122.8 (C-6′), 125.6 (C-1′), 128.1 (C-1″), 137.3 (C-4″), 144.8 (C-3′), 148.3 (C-4′), 153.5 (C-3″ and C-5″), 158.7 (C-2), 159.1 (C-9), 161.1 (C-5), 164.0 (C-7); C-4 not detected. HRESIMS *m/z* 517.1481 (calcd for $C_{27}H_{26}O_9Na$, 517.1475), 495.1635 (calcd for $C_{27}H_{27}O_9$, 495.1635).

4.2.2.8. 3-(3″,5″-Dimethoxy-4″-hydroxyphenyl)-diosmetin 29. To a solution of **25** (40 mg, 0.072 mmol) in anhydrous CH_2CH_2 (5 mL) stirred at −78 °C under nitrogen was added dropwise 1 M boron trichloride in CH_2CH_2 (1 mL). The reaction was stirred for 0.5 h at −78 °C then 16 h at 0 °C. The reaction mixture was taken up in iced water, adjusted at pH 6 with $NaHCO_3$ then extracted with AcOEt. Standard work-up of the organic layer afforded a dry residue (29 mg), which was purified by TLC (silica gel, CH_2CH_2/MeOH 96:4) to give **29** (14 mg, 43%). Light-yellow crystals: mp: 280–283 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 6H, OMe-3″ and 5″), 3.76 (s, 3H, OMe-4′), 6.20 (d, J=2 Hz, 1H, H-6), 6.38 (d, J=2 Hz, 1H, H-8), 6.42 (s, 2H, H-2″ and H-6″), 6.79 (dd, J=8.5, 2 Hz, 1H, H-6′), 6.86 (d, J=8.5 Hz, 1H, H-5′), 6.92 (d, J=2 Hz, 1H, H-2′), 13.04 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.9 (OMe-4′), 56.4 (OMe-3″ and 5″), 93.8 (C-8), 99.1 (C-6), 103.7 (C-10), 109.4 (C-2″ and C-6″), 111.7 (C-5′), 116.5 (C-2′), 120.1 (C-3), 121.8 (C-6′), 122.1 (C-1″), 125.3 (C-1′), 135.7 (C-4″), 146.2 (C-3′), 148.2 (C-3″ and C-5″), 149.8 (C-4′), 157.5 (C-9), 162.0 and 162.1 (C-2 and C-5), 164.7 (C-7), 181.3 (C-4). EIMS *m/z* (%) 452 (M^+, 100), 451 (10).

4.2.2.9. 3-(3″,4″,5″-Trimethoxyphenyl)acacetin 7-benzyl ether 30. Prepared by Suzuki cross-coupling from 136 mg (0.3 mmol) **18**; reaction time 1 h; purification by FC (silica gel, CH_2Cl_2/MeOH 95:5); yield 90% (146 mg). Light-yellow crystals: mp: 184–185 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 6H, OMe-3″ and 5″), 3.80 and 3.85 (2s, 6H, OMe-4′ and 4″), 5.14 (s, 2H, benzyl), 6.45 (s, 2H, H-2″ and H-6″), 6.45 and 6.53 (2d, J=2 Hz, 2H, H-6 and H-8), 6.78 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.3–7.45 (m, 7H, H-2′, H-6′ and benzyl), 12.94 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.2 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.8 (OMe-4″), 70.3 (benzyl), 93.0 (C-8), 98.7 (C-6), 105.2 (C-10), 108.3 (C-2″ and C-6″), 113.5 (C-3′ and C-5′), 120.1 (C-3), 124.6 (C-1′), 127.3, 128.2 and 128.6 (benzyl), 130.9 (C-2′ and C-6′), 135.7 (benzyl), 137.7 (C-4″), 153.3 (C-3″ and C-5″), 157.3 (C-9), 161.1, 161.7 and 162.4 (C-2, C-5 and C-4′), 164.6 (C-7), 181.3 (C-4); C-1″ not detected. HRESIMS *m/z* 541.1883 (calcd for $C_{32}H_{29}O_8$, 541.1862).

4.2.2.10. 3-(3″,4″,5″-Trimethoxyphenyl)acacetin 31. Catalytic hydrogenation of **30** (81 mg, 0.15 mmol) in DMF (Pd–C, rt, 3 h) provided after filtration of the catalyst a dry residue of pure **31** (63 mg, 93%). Pale-yellow crystals: mp: 284–288 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.61 (s, 6H, OMe-3″ and 5″), 3.67 (s, 3H, OMe-4″), 3.76 (s, 3H, OMe-4′), 6.23 (d, J=1.8 Hz, 1H, H-6), 6.44 (d, J=1.8 Hz, 1H, H-8), 6.50 (s, 2H, H-2″ and H-6″), 6.91 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.38 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.97 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.8 (OMe-4′), 56.0 (OMe-3″ and 5″), 60.5 (OMe-4″), 93.8 (C-8), 98.8 (C-6), 102.8 (C-10), 108.6 (C-2″ and C-6″), 113.8 (C-3′ and C-5′), 119.1 (C-3), 124.5 (C-1′), 131.0 (C-2′ and C-6′), 137.0 (C-4″), 152.8 (C-3″ and C-5″), 157.0 (C-9), 160.9 (C-2), 161.0 (C-4′), 161.9 (C-5); C-4, C-7 and C-1″ not detected. HRESIMS *m/z* 473.1243 (calcd for $C_{25}H_{22}O_8Na$, 473.1212), 451.1406 (calcd for $C_{25}H_{23}O_8$, 451.1393).

4.2.2.11. 4′-Methoxy-3-(3″,4″,5″-trimethoxyphenyl)-flavone 32. Prepared by Suzuki cross-coupling from 100 mg (0.3 mmol) **20**; reaction time 4 h; yield 42% (52 mg). White crystals: mp: 170–172 °C (MeOH); ^{1}H

NMR ($CDCl_3$) δ 3.71 (s, 6H, OMe-3″ and 5″), 3.81 (s, 3H, OMe-4′), 3.86 (s, 3H, OMe-4″), 6.47 (s, 2H, H-2″ and H-6″), 6.80 (d, J=8.7 Hz, 2H, H-3′ and H-5′), 7.39 (d, J=8.7 Hz, 2H, H-2′ and H-6′), 7.42 (t, J=7.8 Hz, 1H, H-6), 7.53 (d, J=7.8 Hz, 1H, H-8), 7.70 (t, J=7.8 Hz, 1H, H-7), 8.28 (d, J=7.8 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 54.6 (OMe-4′), 55.9 (OMe-3″ and 5″), 61.0 (OMe-4″), 108.9 (C-2″ and C-6″), 114.0 (C-3′ and C-5′), 117.9 (C-8), 121.4 (C-3), 123.1 (C-10), 124.8 (C-1′), 125.7 (C-6), 126.3 (C-5), 128.3 (C-1″), 132.2 (C-2′ and C-6′), 133.5 (C-7), 137.0 (C-4″), 152.6 (C-3″ and C-5″), 156.0 (C-9), 161.2 (C-4′), 176.8 (C-4); C-2 not detected. ESIMS (+) m/z 441 $[M+Na]^+$, 419 $[M+H]^+$.

4.2.3. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 3. (a) From acacetin **36**.

4.2.3.1. 7-Benzylsulfonylacacetin 37; 7-benzylsulfonyl-6-nitroacacetin 38 and 7-benzylsulfonyl-8-nitroacacetin 39. A solution of acacetin **36** (85 mg, 0.3 mmol) in anhydrous THF (10 mL) was added with triethylamine (0.1 mL) and α-toluenesulfonyl chloride (57 mg, 0.3 mmol), then left at rt for 0.5 h. Standard work-up of the reaction provided the sulfonate **37** (123 mg, 94%). To a solution of **37** (44 mg, 0.1 mmol) in TFA (4 mL) at 0 °C was added 1 equiv HNO_3 53%. The reaction was stirred for 2 h at 0 °C, then taken up in iced water and carefully adjusted at pH 6 with 30% aqueous NaOH. Standard work-up of the reaction then purification of the dried residue by FC (silica gel, CH_2Cl_2/MeOH 99.5:0.5) afforded pure isomers **38** (19 mg, 39%) and **39** (14 mg, 29%).

Compound **37**. Beige-yellowish crystals: mp: 170–173 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 4.58 (s, 2H, benzyl), 6.50 (d, J=1.8 Hz, 1H, H-6), 6.62 (s, 1H, H-3), 6.85 (d, J=1.8 Hz, 1H, H-8), 7.02 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.48 (m, 5H, benzyl), 7.82 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 12.89 (s, 1H, OH-5). ESIMS (+) m/z 899 $[2M+Na]^+$. Compound **38**. Orange-yellow crystals: mp: 198–202 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 4.69 (s, 2H, benzyl), 6.72 (s, 1H, H-3), 7.05 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.07 (s, 1H, H-8), 7.47 (m, 5H, benzyl), 7.85 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 14.05 (s, 1H, OH-5). Compound **39**. Orange-yellow crystals: mp: 193–196 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H, OMe-4′), 4.69 (s, 2H, benzyl), 6.72 (s, 1H, H-3), 6.78 (s, 1H, H-6), 7.05 (d, J=8.8 Hz, 2H, H-3′ and H-5′), 7.48 (m, 5H, benzyl), 7.85 (d, J=8.8 Hz, 2H, H-2′ and H-6′), 13.48 (s, 1H, OH-5). ESIMS (−) m/z 482 $[M-H]^-$.

(b) From naringin **8**

4.2.3.2. 3′-Nitrorhoifolin 41. Rhoifolin **40** was prepared from naringin by the classical procedure (I_2, pyridine, 90 °C, 16 h, 95%).[13] To a solution of rhoifolin **40** (6.87 g, 11.2 mmol) in TFA (50 mL) at 0 °C was added dropwise 1 equiv HNO_3 53%. The reaction was stirred for 2 h at 0 °C, then carefully evaporated at rt with a vacuum system equipped with a KOH trap, and finally dried in a dessicator to provide crude 3′-nitrorhoifolin **41** (quantitative yield) used as it is in the following steps. Lemon-yellow crystals: mp: 220–230 °C; ^{1}H NMR (DMSO-d_6) δ 1.22 (d, J=6 Hz, 3H, Me-6‴), 5.14 (s, 1H, H-1‴), 5.26 (d, J=7 Hz, 1H, H-1″), 6.39 (d, J=1.6 Hz, 1H, H-6), 6.83 (d, J=1.6 Hz, 1H, H-8), 7.03 (s, 1H, H-3), 7.26 (d, J=8.8 Hz, 1H, H-5′), 8.18 (dd, J=8.8, 2.2 Hz, 1H, H-6′), 8.50 (d, J=2.2 Hz, 1H, H-2′). ^{13}C NMR (DMSO-d_6) δ [aglycone moiety] 94.5 (C-8), 99.5 (C-6), 104.9 (C-3), 105.5 (C-10), 119.6 (C-5′), 121.4 (C-1′), 123.4 (C-2′), 132.3 (C-6′), 137.6 (C-3′), 154.4 (C-4′), 156.9 (C-9), 161.0 (C-5), 161.7 (C-2), 162.6 (C-7), 181.8 (C-4); [sugar moiety]: inner glucose 60.4 (C-6″), 69.5[a] (C-4″), 76.4[b] (C-2″), 76.9[b] (C-3″), 77.0[b] (C-5″), 97.6 (C-1″); terminal rhamnose 17.9 (C-6‴), 68.3 (C-5‴), 70.0[a] (C-2‴), 70.2[a] (C-3‴), 72.0 (C-4‴), 100.4 (C-1‴)[a,b] interchangeable. ESIMS (−) m/z 622 $[M-H]^-$.

4.2.3.3. 3′-Nitroapigenin 42; 3′-nitroacacetin 43. Hydrolysis of crude **41** (311 mg, 0.5 mmol) by 11 N HCl (see above **11**→**12**) provided a dry residue of pure 3′-nitroapigenin **42** (131 mg, 83%). Methylation of crude **41** (1.38 g, 2.25 mmol) was performed in DMF (20 mL, stirring at rt) by successive additions of the couple K_2CO_3/MeI until completion of the reaction (1.1 equiv K_2CO_3/0.45 mL MeI for 10 h, 0.55 equiv/0.2 mL for 16 h, 0.22 equiv/0.1 mL for 20 h). The reaction mixture was then filtered and evaporated to dryness. Dry residue was hydrolyzed in 11 N HCl (see above) and furnished after a final crystallization in MeOH 3′-nitroacacetin **43** (541 mg, 73% from **41**). Compound **42**. Lemon-yellow crystals: mp>300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 6.19 (d, J=1.4 Hz, 1H, H-6), 6.50 (d, J=1.4 Hz, 1H, H-8), 6.93 (s, 1H, H-3), 7.25 (d, J=8.8 Hz, 1H, H-5′), 8.19 (dd, J=8.8, 1.9 Hz, 1H, H-6′), 8.51 (d, J=1.9 Hz, 1H, H-2′), 12.78 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 93.4 (C-8), 98.6 (C-6), 103.5 (C-10), 104.1 (C-3), 119.4 (C-5′), 121.5 (C-1′), 122.8 (C-2′), 131.8 (C-6′), 137.5 (C-3′), 153.9 (C-4′), 157.5 (C-9), 161.3 (C-5), 161.6 (C-2), 164.0 (C-7), 181.9 (C-4). ESIMS (−) m/z 314 $[M-H]^-$. Compound **43**. Dark-yellow crystals: mp: 299–300 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 4.01 (s, 3H, OMe-4′), 6.20 (d, J=1.4 Hz, 1H, H-6), 6.53 (d, J=1.4 Hz, 1H, H-8), 7.02 (s, 1H, H-3), 7.51 (d, J=9 Hz, 1H, H-5′), 8.33 (dd, J=9, 2 Hz, 1H, H-6′), 8.54 (d, J=2 Hz, 1H, H-2′), 10.90 (s, 1H, OH-7), 12.75 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 57.0 (OMe-4′), 93.9 (C-8), 98.8 (C-6), 103.3 (C-10), 104.8 (C-3), 114.5 (C-5′), 122.2 (C-1′), 122.5 (C-2′), 131.8 (C-6′), 139.5 (C-3′), 153.8 (C-4′), 156.9 (C-9), 160.9 (C-2), 161.5 (C-5), 164.1 (C-7), 181.5 (C-4). ESIMS (+) m/z 352 $[M+Na]^+$, 330 $[M+H]^+$.

4.2.3.4. 3-Bromo-3′-nitroacacetin 44; 3-bromo-3′-nitroacacetin 7-methyl ether 45; 3-bromo-3′-nitroacacetin 7-benzyl ether 46. Acetylation of **43** (165 mg, 0.5 mmol) then bromination of the dry residue by the two-step sequence (see above **19**→**20**) afforded 3-bromo-3′-nitroacacetin **44** (133 mg, 65% from **43**). Methylation (DMF, 1 equiv K_2CO_3, 10 MeI, rt, 20 h) and benzylation (DMF, 1.05 equiv $KHCO_3$, 3 equiv BnCl, 120 °C, 2 h) of **44** (61 mg, 0.15 mmol for each reaction) provided, respectively, **45** (quantitative yield) and **46** (86%). Compound **44**. Light-yellow crystals: mp: 291–294 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 4.03 (s, 3H, OMe-4′), 6.30 (d, J=1.8 Hz, 1H, H-6), 6.44 (d, J=1.8 Hz, 1H, H-8), 7.57 (d, J=9 Hz, 1H, H-5′), 8.16 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.42 (d, J=2.1 Hz, 1H, H-2′), 11.07 (s, 1H, OH-7), 12.27 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 56.8 (OMe-4′), 93.8 (C-8), 99.0 (C-6), 102.3 (C-10), 114.1 (C-5′), 123.6 (C-1′), 126.1 (C-2′), 135.1

(C-6′), 138.5 (C-3′), 153.9 (C-4′), 157.1 (C-9), 159.1 (C-2), 160.9 (C-5), 164.2 (C-7); C-3 and C-4 not detected. ESIMS (−) *m/z* 408–406 $[M-H]^-$. Compound **45**. Light-yellow crystals: mp: 256–259 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, OMe-7), 4.05 (s, 3H, OMe-4′), 6.43 (s, 2H, H-6 and H-8), 7.23 (d, J=9 Hz, 1H, H-5′), 8.13 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.37 (d, J=2.1 Hz, 1H, H-2′), 12.24 (s, 1H, OH-5). Compound **46**. Amorphous; ^{1}H NMR ($CDCl_3$) δ 4.05 (s, 3H, OMe-4′), 5.10 (s, 2H, benzyl), 6.51 (s, 2H, H-6 and H-8), 7.22 (d, J=9 Hz, 1H, H-5′), 7.3–7.45 (m, 5H, benzyl), 8.11 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.37 (d, J=2.1 Hz, 1H, H-2′), 12.24 (s, 1H, OH-5).

4.2.4. Synthesis of 3-arylflavones analogues of 3.

4.2.4.1. 3′-Nitro-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-methyl ether 33. Prepared by Suzuki cross-coupling from 55 mg (0.13 mmol) **45**; reaction time 3 h; yield 77% (51 mg). Light-yellow crystals: mp: 245–247 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 6H, OMe-3″ and 5″), 3.88 (s, 3H, OMe-4″), 3.91 (s, 3H, OMe-7), 3.97 (s, 3H, OMe-4′), 6.40 (d, J=2 Hz, 1H, H-6), 6.45 (s, 2H, H-2″ and H-6″), 6.51 (d, J=2 Hz, 1H, H-8), 6.92 (d, J=9 Hz, 1H, H-5′), 7.39 (dd, J=9, 2.1 Hz, 1H, H-6′), 8.17 (d, J=2.1 Hz, 1H, H-2′), 12.70 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.2 (OMe-7), 56.7 (OMe-3″ and 5″), 57.1 (OMe-4′), 60.6 (OMe-4″), 92.9 (C-8), 98.8 (C-6), 105.5 (C-10), 107.8 (C-2″ and C-6″), 112.3 (C-5′), 121.1 (C-3), 124.9 (C-1′), 126.2 (C-1″), 127.0 (C-2′), 135.7 (C-6′), 138.3 (C-4″), 139.1 (C-3′), 153.8 (C-3″ and C-5″), 154.2 (C-4′), 157.1 (C-9), 158.4 (C-2), 162.7 (C-5), 166.0 (C-7); C-4 not detected. HRESIMS *m/z* 532.1218 (calcd for $C_{26}H_{23}NO_{10}Na$, 532.1220), 510.1406 (calcd for $C_{26}H_{24}NO_{10}$, 510.1400).

4.2.4.2. 3′-Nitro-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-benzyl ether 34. Prepared by Suzuki cross-coupling from 60 mg (0.3 mmol) **46**; reaction time 2.5 h; yield 84% (59 mg). Pale-yellow crystals: mp: 168–171 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 6H, OMe-3″ and 5″), 3.88 (s, 3H, OMe-4″), 3.96 (s, 3H, OMe-4′), 5.17 (s, 2H, benzyl), 6.45 (s, 2H, H-2″ and H-6″), 6.49 (d, J=2 Hz, 1H, H-6), 6.58 (d, J=2 Hz, 1H, H-8), 6.92 (d, J=9 Hz, 1H, H-5′), 7.35–7.45 (m, 6H, benzyl and H-6′), 8.16 (d, J=2.1 Hz, 1H, H-2′), 12.70 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 56.2 (OMe-3″ and 5″), 56.8 (OMe-4′), 60.9 (OMe-4″), 70.5 (benzyl), 93.1 (C-8), 99.2 (C-6), 105.2 (C-10), 108.0 (C-2″ and C-6″), 113.0 (C-5′), 121.4 (C-3), 124.6 (C-1′), 126.5 (C-1″), 127.4 (C-2′), 128.4, 128.7 and 128.9 (5CH, benzyl), 135.2 (C-6′), 135.6 (C, benzyl), 138.3 (C-4″), 139.2 (C-3′), 153.8 (C-3″ and C-5″), 154.1 (C-4′), 157.3 (C-9), 158.4 (C-2), 162.4 (C-5), 165.0 (C-7), 181.2 (C-4). HRESIMS *m/z* 586.1741 (calcd for $C_{32}H_{28}NO_{10}$, 586.1713).

4.2.4.3. 3′-Amino-3-(3″,4″,5″-trimethoxyphenyl)acacetin 7-methyl ether 47; 3′-amino-3-(3″,4″,5″-trimethoxyphenyl)acacetin 48. Catalytic hydrogenation of **33** (31 mg, 0.06 mmol) and **34** (38 mg, 0.065 mmol) in DMF (Pd–C, rt, 3 h) provided, respectively, after filtration of the catalyst dry residues of pure **47** (29 mg) and **48** (29 mg) in quantitative yields. Compound **47**. Dark-yellow crystals: mp: 225–227 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 6H, OMe-3″ and 5″), 3.83, 3.85 and 3.86 (3s, 9H, OMe-7, 4′ and 4″), 6.36 (d, J=2.2 Hz, 1H, H-6), 6.45 (s, 2H, H-2″ and H-6″), 6.45 (d, J=2.2 Hz, 1H, H-8), 6.60 (d, J=8.5 Hz, 1H, H-5′), 6.70 (dd, J=8.5, 2.1 Hz, 1H, H-6′), 6.82 (d, J=2.1 Hz, 1H, H-2′), 12.93 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.4, 55.6 and 56.0 (OMe-7, 4′, 3″ and 5″), 60.8 (OMe-4″), 92.0 (C-8), 97.9 (C-6), 105.0 (C-10), 108.3 (C-2″ and C-6″), 109.4 (C-5′), 114.9 (C-2′), 120.0 (C-3), 120.7 (C-6′), 124.9 (C-1′), 127.7 (C-1″), 135.8 and 137.7 (C-3′ and C-4″), 148.8 (C-4′), 153.2 (C-3″ and C-5″), 157.4 (C-9), 162.2 and 162.3 (C-2 and C-5), 165.5 (C-7), 181.3 (C-4). HRESIMS *m/z* 502.1491 (calcd for $C_{26}H_{25}NO_8Na$, 502.1478), 480.1655 (calcd for $C_{26}H_{26}NO_8$, 480.1658). Compound **48**. Dark-yellow crystals: mp: 133–135 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.63 (s, 6H, OMe-3″ and 5″), 3.68 (s, 3H, OMe-4″), 3.75 (s, 3H, OMe-4′), 6.22 (d, J=1.8 Hz, 1H, H-6), 6.40 (d, J=1.8 Hz, 1H, H-8), 6.51 (s, 2H, H-2″ and H-6″), 6.52 (dd, J=8.2, 2 Hz, 1H, H-6′), 6.71 (d, J=8.2 Hz, 1H, H-5′), 6.88 (d, J=2 Hz, 1H, H-2′), 13.01 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.2 (OMe-4′), 55.8 (OMe-3″ and 5″), 60.0 (OMe-4″), 93.3 (C-8), 98.7 (C-6), 103.2 (C-10), 108.7 (C-2″ and C-6″), 109.5 (C-5′), 113.5 (C-2′), 118.4 (C-6′), 119.3 (C-3), 124.5 (C-1′), 127.7 (C-1″), 136.9 and 137.2 (C-3′ and C-4″), 147.8 (C-4′), 152.4 (C-3″ and C-5″), 157.0 (C-9), 161.6 and 162.3 (C-2 and C-5), 164.2 (C-7), 180.5 (C-4). HRESIMS *m/z* 488.1309 (calcd for $C_{25}H_{23}NO_8Na$, 488.1321), 466.1548 (calcd for $C_{25}H_{24}NO_8$, 466.1502).

4.3. Synthesis of analogues of the group B

4.3.1. Synthesis of 3-bromoflavones, intermediates for 3-arylflavones analogues of 1 and 2.

4.3.1.1. 3′,4′,5′-Trimethoxyflavone 49; 3-bromo-3′,4′,5′-trimethoxyflavone 50. For the preparation, see compounds **19** and **20**. Compound **49**. (735 mg, 79% from 3 mmol phosphorane). White crystals: mp: 172–174 °C (MeOH), lit.[26] 175 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.96 (s, 6H, OMe-3′ and 5′), 6.77 (s, 1H, H-3), 7.14 (s, 2H, H-3′ and H-5′), 7.43 (t, J=7.9 Hz, 1H, H-6), 7.58 (d, J=8 Hz, 1H, H-8), 7.71 (m, 1H, H-7), 8.24 (d, J=7.9 Hz, 1H, H-5). Compound **50**. (348 mg, 44% from 2 mmol **49**). White crystals: mp: 158–159 °C (MeOH), lit.[25b] 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.96 (s, 6H, OMe-3′ and 5′), 7.10 (s, 2H, H-3′ and H-5′), 7.49 (m, 2H, H-6 and H-8), 7.73 (t, J=8.5 Hz, 1H, H-7), 8.30 (d, J=7.8 Hz, 1H, H-5).

4.3.1.2. Tricetin 3′,4′,5′-trimethyl ether 51; 3-bromotricetin 3′,4′,5′-trimethyl ether 52; 3-bromotricetin 7-benzyl-3′,4′,5′-trimethyl ether 53. Flavone **51** was prepared according Ref. 21 for bromination then benzylation to **52** and **53**, see above **43**→**44**→**46**. Compound **51**. (463 mg, 34% from 4 mmol phosphorane). Lemon-yellow crystals: mp: 270–273 °C (MeOH), lit.[27] 277–278 °C; ^{1}H NMR (DMSO-d_6) δ 3.75 (s, 3H, OMe-4′), 3.90 (s, 6H, OMe-3′ and 5′), 6.22 (d, J=2 Hz, 1H, H-6), 6.56 (d, J=2 Hz, 1H, H-8), 7.04 (s, 1H, H-3), 7.32 (s, 2H, H-3′ and H-5′), 10.81 (s, 1H, OH-7), 12.84 (s, 1H, OH-5). Compound **52**. (296 mg, 59% from 1.2 mmol **51**). Lemon-yellow crystals: mp: 244–247 °C (MeOH); ^{1}H NMR (DMSO-d_6) δ 3.77 (s, 3H, OMe-4′), 3.84 (s, 6H, OMe-3′ and 5′), 6.30 (d, J=2 Hz, 1H, H-6), 6.46 (d, J=2 Hz, 1H, H-8), 7.17 (s, 2H, H-3′ and H-5′), 11.01 (s, 1H, OH-7), 12.32 (s, 1H, OH-5). Compound **53**. (237 mg, 69% from 0.67 mmol **52**). Pale-yellow crystals: mp: 123–126 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H, OMe-4′), 3.95 (s, 6H, OMe-3′ and

5′), 5.13 (s, 2H, benzyl), 6.51 (s, 2H, H-6 and H-8), 7.07 (s, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 12.35 (s, 1H, OH-5).

4.3.2. Synthesis of 3-arylflavones analogues of 1 and 2. Method (a) by Suzuki cross-coupling between a 3-bromoflavone and 4-methoxybenzeneboronic acid according typical procedure.

Method (b) by iron-catalysed Grignard coupling: to a mixture of 3-bromoflavone (0.1 mmol) and $Fe(acac)_3$ (6 mg, 0.015 mmol) in THF (4 mL) between −20 and −30 °C under nitrogen was added arylmagnesium bromide (0.2 mmol). The reaction mixture was stirred at the same temperature for 3 h, then taken up in water and extracted with CH_2Cl_2. Standard work-up then purification by FC and/or TLC led to the expected 3-arylflavone.

4.3.2.1. 3-(4″-Methoxyphenyl)-3′,4′,5′-trimethoxyflavone 54. Preparation by: method (a) (5.5 mg, 13% from 0.1 mmol **50**); method (b) (7.5 mg, 18% from 0.1 mmol **50**); purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5) and TLC (alumina CH_2Cl_2/cyclohexane 1:1). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 6H, OMe-3′ and 5′), 3.80 (s, 3H, OMe-4″), 3.86 (s, 3H, OMe-4′), 6.67 (s, 2H, H-2′ and H-6′), 6.89 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.18 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 7.43 (t, J=7.9 Hz, 1H, H-6), 7.55 (d, J=8.4 Hz, 1H, H-8), 7.71 (m, 1H, H-7), 8.29 (d, J=7.9 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.3 (OMe-4″), 56.0 (OMe-3′ and 5′), 60.9 (OMe-4′), 107.3 (C-2′ and C-6′), 114.1 (C-3″ and C-5″), 117.9 (C-8), 122.2 (C-3), 123.5 (C-10), 125.0 (C-6), 125.5 (C-1″), 126.4 (C-5), 128.2 (C-1′), 132.1 (C-2″ and C-6″), 133.6 (C-7), 139.6 (C-4′), 152.7 (C-3′ and C-5′), 155.9 (C-9), 159.1 (C-4″), 160.7 (C-2), 177.6 (C-4). ESIMS (+) m/z 441 $[M+Na]^+$, 419 $[M+H]^+$.

4.3.2.2. 3-(4″-Methoxyphenyl)tricetin 7-benzyl-3′,4′,5′-trimethyl ether 55. Preparation by method (a); purification by TLC (alumina CH_2Cl_2/MeOH 99:1); (23 mg, 21% from 0.2 mmol **53**). White crystals: mp: 145–148 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 6H, OMe-3′ and 5′), 3.80 (s, 3H, OMe-4″), 3.86 (s, 3H, OMe-4′), 5.16 (s, 2H, benzyl), 6.47 (d, J=2.2 Hz, 1H, H-6), 6.56 (d, J=2.2 Hz, 1H, H-8), 6.64 (s, 2H, H-2′ and H-6′), 6.91 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.16 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 7.3–7.45 (m, 5H, benzyl), 12.90 (s, 1H, OH-5). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe-4″), 56.0 (OMe-3′ and 5′), 60.9 (OMe-4′), 70.4 (benzyl), 93.2 (C-8), 98.8 (C-6), 105.3 (C-10), 107.2 (C-2′ and C-6′), 114.3 (C-3″ and C-5″), 120.6 (C-3), 124.3 (C-1″), 127.5, 128.4 and 128.7 (benzyl), 132.1 (C-2″ and C-6″), 135.8 (benzyl), 139.8 (C-4′), 152.6 (C-3′ and C-5′), 157.4 (C-9), 159.3 (C-4″), 161.1 (C-5), 162.5 (C-2), 164.7 (C-7), 181.7 (C-4); C-1′ not detected. ESIMS (+) m/z 563 $[M+Na]^+$, 541 $[M+H]^+$.

4.3.2.3. 3-(3″-Benzyloxy-4″-methoxyphenyl)tricetin 7-benzyl-3′,4′,5′-trimethyl ether 56. Preparation by method (b); purification by FC (silica gel CH_2Cl_2/MeOH 99:1) and TLC (silica gel cyclohexane/acetone 1:1); (15 mg, 12% from 0.2 mmol **53**). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.60 (s, 6H, OMe-3′ and 5′), 3.85 and 3.88 (2s, 6H, OMe-4′ and 4″), 5.03 and 5.16 (2s, 4H, benzyls), 6.48 (d, J=2.2 Hz, 1H, H-6), 6.53 (d, J=2.2 Hz, 1H, H-8), 6.57 (s, 2H, H-2′ and H-6′), 6.7–7.0 (m, 3H, H-2″, H-5″ and H-6″), 7.2–7.5 (m, 10H, benzyls), 12.90 (s, 1H, OH-5).

4.3.2.4. Tricetin 7-benzyl-3′,4′,5′-trimethyl ether 57. Pale-yellow crystals: mp: 203–205 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H, OMe-4′), 3.95 (s, 6H, OMe-3′ and 5′), 5.15 (s, 2H, benzyl), 6.48 (d, J=2 Hz, 1H, H-6), 6.59 (d, J=2 Hz, 1H, H-8), 6.78 (s, 1H, H-3), 7.09 (s, 2H, H-3′ and H-5′), 7.35–7.45 (m, 5H, benzyl), 12.72 (s, 1H, OH-5).

4.3.2.5. 3-(4″-Methoxyphenyl)tricetin 3′,4′,5′-trimethyl ether 58; 3-(3″-hydroxy-4″-methoxyphenyl)tricetin 3′,4′,5′-trimethyl ether 59. Catalytic hydrogenation of **55** (15 mg, 0.028 mmol) and **56** (15 mg, 0.023 mmol) in THF (Pd–C, rt, 3 h) provided, respectively, after filtration of the catalyst dry residues of pure **58** (12 mg) and **59** (10 mg) in quantitative yields. Compound **58**. Amorphous; ^{1}H NMR (DMSO-d_6) δ 3.56 (s, 6H, OMe-3′ and 5′), 3.66 (s, 3H, OMe-4′), 3.75 (s, 3H, OMe-4″), 6.24 (d, J=2.1 Hz, 1H, H-6), 6.49 (d, J=2.1 Hz, 1H, H-8), 6.69 (s, 2H, H-2′ and H-6′), 6.93 (d, J=8.6 Hz, 2H, H-3″ and H-5″), 7.13 (d, J=8.6 Hz, 2H, H-2″ and H-6″), 10.89 (s, 1H, OH-7), 12.92 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.1 (OMe-4″), 55.6 (OMe-3′ and 5′), 60.0 (OMe-4′), 93.8 (C-8), 98.8 (C-6), 103.3 (C-10), 107.2 (C-2′ and C-6′), 113.6 (C-3″ and C-5″), 119.8 (C-3), 124.1 (C-1″), 127.2 (C-1′), 132.1 (C-2″ and C-6″), 138.9 (C-4′), 152.1 (C-3′ and C-5′), 157.1 (C-9), 158.7 (C-4″), 160.8 (C-2), 161.5 (C-5), 164.4 (C-7), 180.8 (C-4). ESIMS (+) m/z 473 $[M+Na]^+$, 451 $[M+H]^+$. Compound **59**. Amorphous; ^{1}H NMR (DMSO-d_6) δ 3.58 (s, 6H, OMe-3′ and 5′), 3.66 (s, 3H, OMe-4′), 3.75 (s, 3H, OMe-4″), 6.21 (d, J=2.1 Hz, 1H, H-6), 6.46 (d, J=2.1 Hz, 1H, H-8), 6.58 (dd, J=8.2, 2 Hz, 1H, H-6″), 6.64 (d, J=2 Hz, 1H, H-2″), 6.73 (s, 2H, H-2′ and H-6′), 6.90 (d, J=8.2 Hz, 1H, H-5″), 12.94 (s, 1H, OH-5). ^{13}C NMR (DMSO-d_6) δ 55.5 (OMe-3′, 5′ and 4″), 60.0 (OMe-4′), 93.5 (C-8), 98.3 (C-6), 107.1 (C-2′ and C-6′), 112.3 (C-5″), 118.5 (C-2″), 121.9 (C-6″), 124.8 (C-1″), 127.4 (C-1′), 139.2 (C-4′), 146.4 (C-3″), 147.7 (C-4″), 152.4 (C-3′ and C-5′), 161.0 (C-2); C-3, C-4, C-5, C-7, C-9 and C-10 not detected. ESIMS (+) m/z 489 $[M+Na]^+$, 467 $[M+H]^+$.

4.4. Synthesis of analogues of the groups C and D

4.4.1. One-pot access to keto-enols 60 and 61 by esterification then Baker–Vankataraman rearrangement.

4.4.1.1. 3′,4′,5′-Trimethoxy-2-hydroxy-dibenzoylmethane 60 (mixture of keto-enol and β-diketone tautomers 82/18); 4′-methoxy-2-hydroxy-dibenzoylmethane 61. A solution of 2′-hydroxyacetophenone (1.36 g, 10 mmol) in dry pyridine (10 mL) at 0 °C under nitrogen was added with the adequate aroyl chloride (15 mmol), and the reaction mixture stirred for 2.5 h at rt. Powdered dry KOH (1.68 g, 30 mmol) was added and the reaction heated at 100 °C for 2 h, then same quantity of KOH was added again and the mixture heated for a further 1 h. After cooling, the mixture was poured into water, adjusted to pH 6 with 1 N HCl and extracted by CH_2Cl_2. Standard work-up of the organic layer and crystallization in MeOH provided the intermediates **60** (1.23 g, 37%) and **61** (925 mg, 34%). Compound **60**. Lemon-yellow crystals: mp: 134–136 °C (MeOH), lit.[26] 136 °C; ^{1}H NMR ($CDCl_3$)

characteristic signals at δ 4.70 (s, CH_2) and 12.12 (s, phenol) for the β-diketone form; at 6.84 (s, CH–C═O), 12.20 (s, phenol) and 15.84 (s, enol) for the enol tautomer. Compound **61**. Lemon-yellow crystals: mp: 110–111 °C (MeOH), lit.[26] 114 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, OMe-4′), 6.89 (d, H-3), 6.97 and 7.45 (m, H-4 and H-5), 6.98 (d, H-3′ and 5′), 7.76 (d, H-6), 7.92 (d, H-2′ and 6′), 6.77 (s, CH–C═O), 12.17 (s, phenol), 15.80 (s, enol).

4.4.2. Knoevenagel condensation to crude 3-aroylflavanones then dehydrogenation by SeO_2 to 65, 66 and 67. General procedure: compounds **60** or **61** (0.5 mmol) and adequate aromatic aldehyde (0.55 mmol) were dissolved in EtOH (5 mL) by heating under reflux. Piperidine (12 mg, 0.14 mmol) was then added, and the reaction stirred under reflux for 5 h. The reaction mixture was evaporated to dryness and used as it is in the following step. Fifth of the dried residue and SeO_2 (in equal weight) were stirred in dioxane at reflux for 6 h under nitrogen. Reaction mixture was filtered, and evaporated to dryness. Dry residue was then purified by FC and crystallization.

4.4.2.1. 4′-Methoxy-3-(3″,4″,5″-trimethoxybenzoyl)-flavone 65. Preparation from **60** and *p*-anisaldehyde; purification by FC (silica gel CH_2Cl_2/MeOH 99:1); (16 mg, 36% from **60**). White crystals: mp: 90–92 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 9H, OMe-4′, 3″ and 5″), 3.89 (s, 3H, OMe-4″), 6.89 (d, J=8.9 Hz, 2H, H-3′ and H-5′), 7.20 (s, 2H, H-2″ and H-6″), 7.46 (t, J=8 Hz, 1H, H-6), 7.59 (d, J=8.1 Hz, 1H, H-8), 7.64 (d, J=8.9 Hz, 2H, H-3′ and H-5′), 7.75 (m, 1H, H-7), 8.24 (dd, J=8, 1.4 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.4 (OMe-4′), 56.3 (OMe-3″ and 5″), 60.9 (OMe-4″), 107.0 (C-2″ and C-6″), 114.3 (C-3′ and C-5′), 118.0 (C-8), 121.3 (C-3), 123.2 (C-10), 123.9 (C-1′), 125.5 (C-6), 126.1 (C-5), 130.2 (C-2′ and C-6′), 132.3 (C-1″), 134.2 (C-7), 143.3 (C-4″), 153.2 (C-3″ and C-5″), 156.0 (C-9), 162.0 and 162.2 (C-2 and C-4′), 176.3 (C-4), 192.8 (C═O). ESIMS (+) *m*/*z* 915 $[2M+Na]^+$, 469 $[M+Na]^+$.

4.4.2.2. 3′-Hydroxy-4′-methoxy-3-(3″,4″,5″-trimethoxybenzoyl)flavone 66. Preparation from **60** and isovanillin; purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5); (18 mg, 40% from **60**). Amorphous; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 6H, OMe-4′, 3″ and 5″), 3.89 (s, 6H, OMe-4′ and 4″), 6.78 (d, J=8.5 Hz, 1H, H-5′), 7.16 (dd, J=8.5, 2.2 Hz, 1H, H-6′), 7.19 (s, 2H, H-2″ and H-6″), 7.33 (d, J=2.2 Hz, 1H, H-2′), 7.45 (m, 1H, H-6), 7.58 (d, J=7.8 Hz, 1H, H-8), 7.75 (m, 1H, H-7), 8.26 (dd, J=7.9, 1.5 Hz, 1H, H-5). ESIMS (+) *m*/*z* 947 $[2M+Na]^+$, 485 $[M+Na]^+$.

4.4.2.3. 3-(4″-Methoxybenzoyl)-3′,4′,5′-trimethoxyflavone 67. Preparation from **61** and 3,4,5-trimethoxybenzaldehyde; purification by FC (silica gel CH_2Cl_2/MeOH 98.5:1.5); (24 mg, 54% from **61**). White crystals: mp: 139–141 °C (MeOH); ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 6H, OMe-3′ and 5′), 3.77 (s, 6H, OMe-4′ and 4″), 6.90 (d, J=8.9 Hz, 2H, H-3″ and H-5″), 6.91 (s, 2H, H-2′ and H-6′), 7.46 (t, J=7.9 Hz, 1H, H-6), 7.60 (d, J=8.1 Hz, 1H, H-8), 7.75 (m, 1H, H-7), 7.94 (d, J=8.9 Hz, 2H, H-3″ and H-5″), 8.24 (dd, J=7.9, 1.5 Hz, 1H, H-5). ^{13}C NMR ($CDCl_3$) δ 55.5 (OMe-4″), 56.1 (OMe-3′ and 5′), 60.9 (OMe-4′), 106.1 (C-2′ and C-6′), 114.1 (C-3″ and C-5″), 118.0 (C-8), 122.6 (C-3), 123.3 (C-10), 125.6 (C-6), 126.1 (C-5), 126.7 (C-1′), 130.4 (C-1″), 131.8 (C-2″ and C-6″), 134.2 (C-7), 140.5 (C-4′), 153.2 (C-3′ and C-5′), 156.0 (C-9), 161.5 (C-2), 164.2 (C-4″), 176.4 (C-4), 192.0 (C═O). ESIMS (+) *m*/*z* 915 $[2M+Na]^+$, 469 $[M+Na]^+$.

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