European Journal of Medicinal Chemistry 44 (2009) 2497–2505

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Diversity-oriented synthesis of furo[3,2-*f*]chromanes with antimycobacterial activity

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ARTICLE INFO

Article history:
Received 16 August 2008
Received in revised form
1 December 2008
Accepted 16 January 2009
Available online 29 January 2009

Keywords:
Antimycobacterial
Tuberculosis
Chromanes
Benzofuranes

ABSTRACT

We previously reported the synthesis and the antimycobacterial activity of 4-(7,7-dimethyl-7*H*-furo[3,2-*f*]chromen-2-yl)pyridine. From this result, we sought to design simple synthetic accesses to related structures allowing the preparation of a diverse set of analogues. Two approaches were investigated. From 3-(2-bromo-7,7-dimethyl-8,9-dihydro-7*H*-furo[3,2-*f*]chromen-1-yl)propyl acetate, we prepared 2-arylated derivatives *via* Suzuki–Miyaura reactions between this bromine-bearing compound and various arylboronates. Moreover, and even more simple, we prepared the ((6-hydroxy-2,2,7,8-tetramethylchroman-5-yl)methyl)triphenylphosphonium salt *via* a selective bromination of 2,2,5,7,8-pentamethylchroman-6-ol. From this salt, a two stage Wittig reaction with an array of activated acids allowed the quick preparation of many analogues. The biological evaluation of the effect of these compounds on the growth of *Mycobacterium bovis* as well as *Mycobacterium tuberculosis* pointed out a fourfold improvement of the antimycobacterial properties for one of the compounds made. However, the many analogues which inhibited the growth of *M. tuberculosis* in the 0.6–5 μg/mL range turned out to be also cytotoxic on VERO cells growth at the same concentration range.

As described in a preceding paper [1], in the course of our researches [2–5] on the synthesis of analogues of the specific antimycobacterial the chromane-bearing compound **1** [6], we have prepared the furo[3,2-*f*]chromene derivatives **2a**,**b** which displayed better inhibition activity on *Mycobacterium tuberculosis* growth than the initial hit. Our first syntheses of analogues of compounds **2a**,**b** allowed the determination of some of the structure–activity relationships and confirmed the potential interest of this new series [1]. However, it became apparent that simpler synthetic access allowing the quick preparation of an array of analogues featuring a diverse set of substituents would have been useful for a full exploration of the structure–activity relationships of these series. Inherent to this aim was the design of synthetic pathways in which the variable substituents are introduced in the final steps of the synthesis, much preferably the last one. We wish to report here two original approaches which are using compound **3** or the commercially available chromane **4** as starting material for the preparation of diversity-oriented analogues of compounds **2a**,**b** (Fig. 1).

In the first approach, we reduced the chromene ring of the readily available compound **3** [1], using hydrogen and palladium over charcoal, to obtain compound **5**. The other pyran ring could then selectively opened in boiling acetic acid containing hydrogen chloride. This gave an access to the furo[3,2-*f*]chromane derivative **6**. The following selective halogenation of its carbon 2 was possible using *N*-bromosuccinimide and provided an access to the key precursor **7**. The Suzuki–Miyaura aryl–aryl coupling reaction of the hindered brominated compound **7** and 4- or 3-pyridylboronic derivatives was then investigated. After few trials, the rewarding use of the reported [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium as a precatalyst and cesium carbonate as a base in a water/dioxane solution [7, 8] allowed the preparation, in acceptable 60 and 55% yields, of the analogues **8a**,**b**. The corresponding pyridyl-bearing alcohols **9a**,**b** were then obtained by the methanolysis of their acetyl moiety (Scheme 1).

In a second approach, we made good use of a synthetic scheme initially reported for the preparation of benzofuranes [9]

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doi:10.1016/j.ejmech.2009.01.017

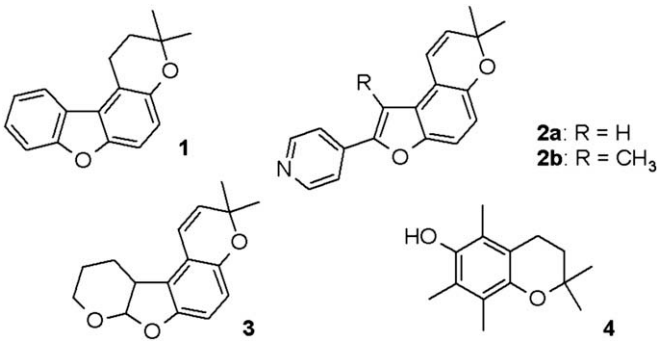


Fig. 1.

and further developed for the preparation of furo[3,2-*f*]chromanes [10]. Starting from the commercially available chromanol **4**, a regioselective bromination [11,12] of its C5 methyl gave compound **10**. This was followed by the preparation of the phosphonium salt **11**. This salt could then react with an array of activated acids to give the 2-arylated furo[3,2-*f*]chromanes **13a–i** via the corresponding esters **12** in a two stage process [9,13]. As we extended this route, various procedures, fully described in the experimental part, were used. In the first stage, which led to the intermediate esters **12**, acyl chlorides, as well as dicyclohexylcarbodiimide-activated acids were successfully reacted with the phosphonium salt **11**. The cyclization of these intermediates was then achieved by the addition of triethylamine to the medium and extensive heating. It became apparent that a stock solution of the phosphonium **11** in dichloromethane could be used and that the rather long heating time required for cyclization of the intermediate esters could be undertaken in this solvent at temperature as high as 65 °C, provided it was done in a sealed tube (Scheme 2).

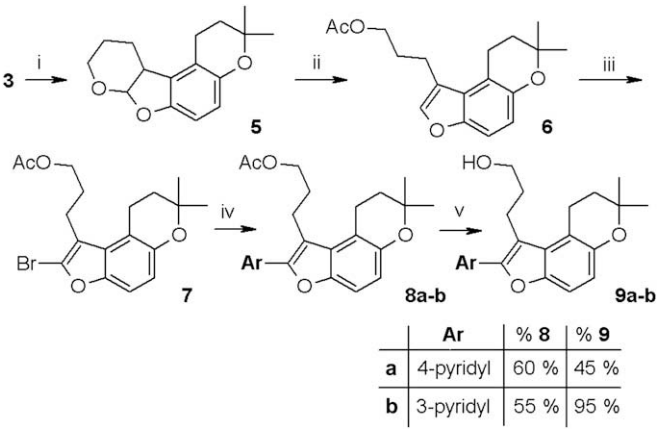
The reaction yields for the preparation of compounds **13a–j** were observed to vary between 5.5 and 90% depending on the acid considered and the coupling method used. We did not try to optimize the fairly low 5.5% yield of compound **13f**, which is likely to be due to the instability of the intermediate malonyl ester. By using a three-stage process, we also prepared the amide-bearing compound **14a–c** from compound **11**, succinic anhydride, various secondary amines and DCC. Further refinement of this strategy led us to isolate the phosphonium salt **11** which, contrary to what has been reported [10], turns out to be perfectly stable; if made from compound **4** in a one pot procedure using *N*-bromosuccinimide. This is probably due to the fact

	R	% 13a-j
a	3-pyridyl	38 %
b	CH_2OAc	80 %
c	4-pyridyl	80 %
d	2-chloro-5-pyridyl	90 %
e	4-chlorobenzyl	50 %
f	CH_2CN	5.5 %
g	2-pyridyl	80 %
h	3-CH_2-pyridyl	27 %
i	2-pyrazinyl	52 %
j	2-tetrahydrofuranyl	60 %

Scheme 2. (i) Br_2 cyclohexane. (ii) PPh_3, CH_2Cl_2 or cyclohexane. (iii) RCOCl or RCOOH, DCC; NEt_3. (iv) NEt_3, heat.

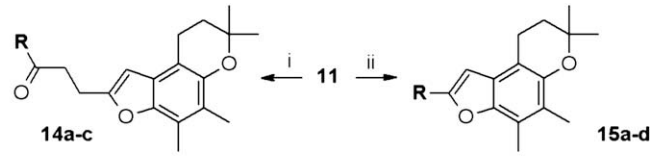
that we avoided the use of bromine and thus obtained compound **10** free of traces of hydrogen bromide. Moreover, we could replace the rather long heating time by using a microwave oven. This allowed the subsequent synthesis of analogues **15a–d** from the corresponding acylchlorides or the acids using a much simplified procedure involving DCC and hydroxybenzotriazole in acetonitrile (Scheme 3). A similar use of microwave heating has actually been reported very recently for the synthesis of benzofuranes from (2-hydroxybenzyl)-triphenylphosphonium salt and various acids activated by trichlorotriazine [14].

As shown in Scheme 4, some subsequent modifications were made. The oxidation of compound **13a** with cerium ammonium nitrate turned out to lead to 74% of the ketone **16** whereas its oxidation with 3-chloroperbenzoic acid gave the *N*-oxide derivative **17**. A nucleophilic substitution reaction with the chloropyridine-bearing derivative **13d** gave the far more soluble diaminated analogue **18**. Also from this chloropyridine-bearing derivative **13d**, a palladium-catalysed substitution reaction with zinc cyanide [15] led to the nitrile-bearing analogue **19**. The first element of structure–activity relationship obtained led us to prepare a few other derivatives from compound **19**. For instance its nitrile moiety was transformed in a tetrazole *via* a (slow) cycloaddition reaction with hydrazoic acid generated *in situ* to give compound **20**. Moreover,



	Ar	% 8	% 9
a	4-pyridyl	60 %	45 %
b	3-pyridyl	55 %	95 %

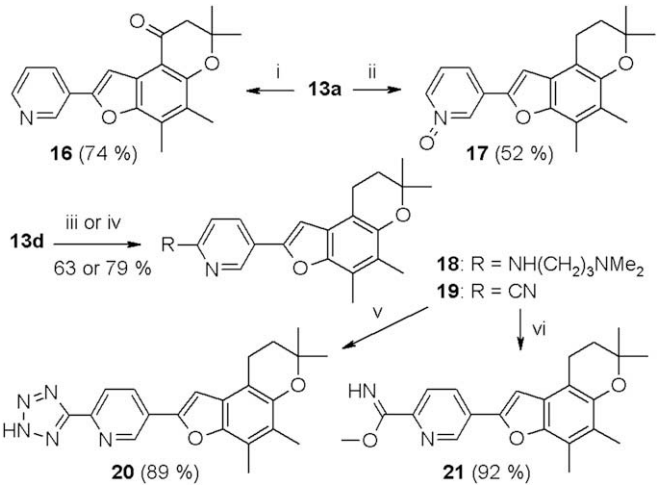
Scheme 1. (i) HCOOH, NH_3, Pd/C ethanol reflux. (ii) AcOH, HCl reflux. (iii) NBS, EtOH. (iv) $ArB(OH)_2$, Pd dppf, dioxane–water, Cs_2CO_3, 80 °C. (v) MeONa/MeOH.



	R	% 14
a	Morpholine	22 %
b	4-Methylpiperazine	39 %
c	Pyrrolidine	6 %

	R	% 15
a	3-Pyridyl-CH=CH-	22 %
b	3-Pyridyl-CH_2-CH_2-	10 %
c	2-Thiophenyl-	26 %
d	2-Thiophenyl-CH_2-	33 %

Scheme 3. (i) Succinic anhydride, amine, CH_2Cl_2, then DCC; **11**, NEt_3, heat. (ii) RCOOH, DCC, HOBt, (or RCOCl) NEt_3, MeCN, 120 °C (microwave).



Scheme 4. (i) $(NH_4)_2Ce(NO_3)_6$, MeCN, 25 °C. (ii) mCpBA, CH_2Cl_2, 25 °C. (iii) Amine, reflux. (iv) ZnCN, $PdCl_2$dppf, DMA, 120 °C. (v) NaN_3, NEt_3, HCl, toluene, 80 °C. (vi) tBuOK, MeOH, 25 °C.

the imidoester **21** was easily prepared *via* the addition of methanolate on the nitrile function of compound **19** [16].

1. Biological results and discussion

The antimycobacterial activity was screened most often on *Mycobacterium bovis* BCG as well as on the virulent strain *M. tuberculosis* H37Rv, using the new Microdilution Resazurin Assay (MRA) [17]. The minimal inhibitory concentration (MIC_{95}) is defined as the amount of compound required for >95% inhibition of bacterial growth is provided in microgram per millilitre. The compounds found to be the most active against *M. tuberculosis* were further evaluated for their cytotoxicity on mammalian VERO cell lines using the dimethylthiazolyldiphenyl tetrazolium (MTT)-based assay. All these results are summarized in Table 1.

Even if the solubility remains an issue with many compounds of this series, some of the antimycobacterial activity obtained point out interesting structure–activity relationships. For instance, when compared to compound **2a**, a fourfold improvement of antimycobacterial effect was seen for compound **21**. However, the cytotoxicity measurement of some of the most active compounds dampened very much these encouraging results. Unfortunately, the most effective antimycobacterials (compounds **2a**,**b**, **8a**, **13h**, **15b**, **17**, **18** and **21**) were also cytotoxic at the same concentration range. Moreover, an SOS-chromotest pointed out that, amongst these analogues, compound **18** is also mutagenic. As a selectivity of action on the mycobacteria genus had been observed [6] for compound **1**, the inhibition of the growth of *Staphylococcus aureus*, *Escherichia coli* and *Candida tropicalis* by these analogues was also measured. None were found active on Gram-negative *E. coli*, however the cytotoxic compounds (**2a**,**b**, **8a**, **13h**, **15b**, **17**, **18** and **21**) had an effect on the Gram-positive *S. aureus* growth with MIC_{90} between 5 and 18 μg/mL. Moreover, compound **18**, the only mutagenic one, had a measurable diameter of inhibition on the growth of *C. albicans*. Interestingly, the structurally related antioxidant α-tocopherol as well as the smaller chromanol **4** inhibited *M. tuberculosis* growth. Concerning α-tocopherol, this antimycobacterial effect had actually been previously reported [18–20]. In any case, this inhibition suggests an antioxidant-based mechanism of action for these antibacterials as they share a common "oxy"-chromane ring system. However, this is very much a hypothesis as the fairly lipophilic antioxidant 2,6-bistertbutyl*p*cresol (BHT) was devoid of antimycobacterial activity. In conclusion, from the structure of the remarkably selective antimycobacterial compound **1** reported in 2006 [6], our research program on the design of synthetic access to structural analogues proved quite fruitful from the organic chemistry point of view [1–4]. However, the antimycobacterial agents previously made, although sometime of interest, turned out to be cytotoxic as well [3] or were not really better than the starting point [4]. The present investigation in chemistry provides two original synthetic accesses to 7*H*-furo[3,2-*f*]chromene analogues of **2a**,**b**. From our work on the chemistry of formylbenzoquinone [1], two successive cycloadditions led to compound **5**. This was then transformed into the brominated precursor **7** which allowed for a quick access to chemically diverse compounds using the Suzuki–Miyaura palladium-catalysed aryl–aryl coupling reaction. Further investigations led us to the use of the readily available phosphonium salt **11** featuring a chromane ring system. This provided a single step access to many derivatives featuring the 7*H*-furo[3,2-*f*]chromen ring system with a multitude of possible substituents on carbon C-2 as well as two methyls on the central ring. Unfortunately, the many analogues made which inhibit the growth of *M. tuberculosis* in the low microgram per millilitre range are also cytotoxic at this concentration. Interestingly, the lipophilic thiophene-bearing compound **15c** and to a lesser extent compound **15d** seem to have a selective action on *M. tuberculosis* (assays of these two compounds on *Mycobacterium. smegmatis* growth also showed a lack of effects even at a 100 μg/mL concentration). These facts, especially the cytotoxicity observed, will have to be

Table 1
In vitro biological assays.

Compound	MIC_{95}[a] *M. bovis*	MIC_{95}[a] *M. tuberculosis*	IC_{50} (VERO cells)
Isoniazid	0.4	0.25	>500
α-Tocopherol	N.D.	10	N.D.
1	N.D.	10	100
2a	6.2	2.5	8.7
2b	6.2	5	12.8
3	N.D.	250	N.D.
4	N.D.	10	N.D.
7	50	>10	N.D.
8a	3.1	5	14.9
8b	12.5	5	17.5
9a	12.5	5	>25
9b	6.2	5	>25
13a	3.1	5	N.D.
13b	>100	10	N.D.
13c	3.1	2.5	5.1
13d	>100	>10	N.D.
13e	>100	25	>100
13f	N.D.	>10	N.D.
13g	>100	100	N.D.
13h	6.2	3	6.4
13i	25	10	N.D.
13j	N.D.	>10	N.D.
14a	>100	10	N.D.
14b	N.D.	>10	N.D.
14c	N.D.	10	N.D.
15a	6.2	5	>100
15b	3.1	5	7.3
15c	>100	6.2	>100
15d	>100	12.5	ND
16	N.D.	>10	N.D.
17	12.5	5	5.6
18	6.2	3	1.6
19	ND	>10	N.D.
20	25	10	N.D.
21	6.2	0.6	3.6

ND: not determined.
[a] All the values provided are in μg/mL.

taken into account in any design of further analogues of compound **1** or **2a**,**b**.

2. Experimental part

2.1. Chemistry

A Biotage Initiator 2 microwave oven was used for reactions requiring microwave irradiations. The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400 MHz and 100 MHz, respectively. Unless otherwise noted, $CDCl_3$ was the solvent used. Shifts (δ) are given in ppm with respect to the TMS signal and coupling constants (J) are given in Hertz. Column chromatography was performed either with Merck silica gel 60 (0.035–0.070 mm) or neutral alumina containing a suitable proportion of water, using a solvent pump operating at pressure between 2 and 7 bar (25–50 mL/min) and an automated collecting system driven by a UV detector set to 254 nm unless stated otherwise (i.e. if ethyl acetate was used then it would be set to 280 nm). Sample deposition was always carried out by absorption of the mixture to be purified on a small amount of the solid phase followed by its deposition on the top of the column. The low resolution mass spectra were obtained on an Agilent 1100 serie LC/MSD system using an atmospheric electrospray ionisation system and the high resolution mass spectroscopy spectra (HRMS) were obtained using a Waters Micromass Q-Tof with an electrospray ion source.

2.2. Biology

2.2.1. Strains

Reference strains of *E. coli* (CIP188631), *S. aureus* (ATCC6538), *C. tropicalis* (ATCC66029), *M. smegmatis* mc2155, *M. tuberculosis* H37Rv (Institut Pasteur, Paris, France), *M. bovis* BCG (Pasteur), *E. coli*, PQ37 (F^- *thr leu his-4 pyrD thi galE galK lac*Δ*U169 srl300*::Tn10 *rpoB rpsL uvrA rfa trp*::*Muc*$^+$ *sfiA*::*Mud* (Ap, *lac*) *cts*) were obtained from the Collection of the Institut Pasteur.

All the biological assays were made in duplicate in two independent experiences, for this reason no standard deviation could be calculated.

2.2.2. MIC determinations for mycobacteria

MICs were determined using the new Microdilution Resazurin Assay (MRA) [17]. Resazurin salt powder (Sigma) was prepared at 0.01% (wt/vol) in distilled water, sterilized by filtration through a 0.22 μm membrane and stored at 4 °C for a week. Drug stock solutions were prepared in dimethylsulfoxide (DMSO) at a concentration of 50 mg/mL and frozen until used. The inocula were prepared from *M. tuberculosis* H37Rv or from *M. bovis* BCG strains grown in Dubos medium supplemented with 10% ADC enrichment (Difco). One microliter of twofold serial dilutions of each drug were prepared in 100 μL of Dubos medium directly in 96-well plates at concentrations from 500 μg/mL to 0.9 μg/mL. Growth controls containing DMSO and isoniazid (from 1 μg/mL to 1 ng/mL) were also included. The plates were covered, sealed and incubated at 37 °C. After 6 days (or 8 for *M. bovis*), 30 μL of resazurin solution was added to each well and plates were allowed to incubate at 37 °C for an additional 24 h. A change from blue to pink indicates reduction of resazurin and therefore bacterial growth. The MIC was defined as the lowest drug concentration that prevented this colour change.

2.2.3. Cytotoxicity evaluation

VERO cell lines were maintained in DMEM supplemented with 5% Foetal calf serum (FCS), at 37 °C in air with 5% CO_2. Proliferating cells were seeded in 96-well microtitration plates at a density of 10^5 cells/mL, which were further incubated for 24 h at 37 °C under 5% CO_2 in air before each assay. Various concentrations of solutions of compounds in 1% DMSO were added and then incubated for 48 h as described above. At the end of this, 20 μL of dimethylthiazolyldiphenyl tetrazolium bromide solution (MTT, Sigma) (5 mg/mL) was added to each well and further incubated for 4 h at 37 °C to allow the formation of formazan. The crystals of formazan were then dissolved with 100 μL of a freshly prepared solution of sodium dodecyl sulfate (SDS) 10% (15 mL) and HCl 1 N (150 μL). The optical density of each well was measured at 595 nm using a multi-well plate reader. The 50% inhibition concentration was then determined by curve fitting.

2.2.4. MIC determination for bacteria

Pre-cultures of the tested microorganisms *E. coli* or *S. aureus* were made by inoculating 10 mL of Luria-Bertani (LB) and incubating for 24 h. A culture suspension was made by 1/1000 dilution from preculture and seeded in 96-well microtitration plates. One microliter of twofold serial dilutions of each drug was prepared in 100 μL of LB. The plates were incubated at 37 °C. After 24 h, the optical density of each well was measured at 595 nm using a multiplate reader. The 90% inhibition concentrations for the most active compounds were determined by curve fitting. Tetracycline was used as positive control.

2.2.5. Antifungal activity

Activities of the more active compounds were evaluated on the growth of *C. tropicalis* using the standardized filter paper disk (6 mm non-impregnated disk; Antibiotica assay discs, Grade 2668 Schleider and Schuell) diffusion method according to the Kirby–Bauer method [21]. Briefly, a suspension of *C. tropicalis* was spread on solid Sabouraud media plates (20 mL). Filter paper discs were impregnated with 10 μL of serial dilutions in dimethylsulfoxide (DMSO, Sigma) of the compounds and placed onto the solid media plates. The diameter of inhibition was measured after 24 h of incubation at 30 °C. Itraconazole was used as positive control.

2.2.6. Genotoxicity assay: SOS-chromotest

The capacity of the drugs to induce DNA damage is monitored with the SOS-chromotest [22]. This test is based on a genetically engineered *E. coli* strain, PQ37 licensed from the Institut Pasteur, which measures the primary response of a cell to genotoxic damage. This strain harbours the *lacZ* gene under the control of *sfiA*, a gene involved in the SOS response. DNA damage results in the activation of the SOS system which in turn induces the transcription and synthesis of β-galactosidase. This enzyme is detected by a chromogenic reaction with the substrate X-gal.

2.3. 3,3-Dimethyl-2,3,9,10,11,11a-hexahydro-1H,7aH-4,7,8-trioxabenzo[c]fluorene (**5**)

Compound **3** (2.89 g, 0.011 mol) was dissolved in ethanol (300 mL), ammonium formate (1.41 g, 0.022 mol) and 10% palladium over charcoal (0.59 g, 0.5 mmol) were then added. This suspension was heated to reflux for 40 min before filtering it. The concentrated filtrate yielded compound **5** as an oil, almost invisible on TLC using an UV lamp, which was used in the next step without further purification. ^{1}H NMR ($CDCl_3$): 1.31 (s, 3H), 1.35 (s, 3H), 1.64 (m, 3H), 1.79 (m, 2H), 2.11 (m, 1H), 2.69 (t, 2H, $J = 6.7$), 3.11 (s, 1H), 3.87 (m, 2H), 5.84 (d, 1H, $J = 6.3$), 6.58 (d, 1H, $J = 8.5$), 6.63 (d, 1H, $J = 8.5$). ^{13}C NMR ($CDCl_3$): 20.3, 21.3, 26.3, 27.3, 27.8, 32.7, 38.0, 61.6, 73.7, 104.9, 109.0, 116.5, 118.3, 129.3, 148.5, 150.4.

2.4. 3-(7,7-Dimethyl-8,9-dihydro-7H-furo[3,2-f]chromen-1-yl)-propyl acetate (**6**)

The crude compound **5** was refluxed in acetic acid (100 mL) containing 2 N hydrochloric acid (5 mL) for 2 h. The resulting solution was concentrated to dryness and diluted in dichloromethane. The organic phase was washed with saturated solution of sodium hydrogenocarbonate then water, dried over sodium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 6:1) to yield compound **6** as a solid (2.69 g, 79% from compound **3**). m.p. = 82 °C. HRMS (ES) calc. for: $C_{18}H_{22}O_4Na$ 325.1416; found: 325.1473. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.88 (t, 2H, $J = 6.7$), 2.04 (m, 2H), 2.09 (s, 3H), 2.86 (m, 2H), 3.10 (m, 2H), 4.21 (t, 2H, $J = 6.7$), 6.7 (d, 1H, $J = 8.8$), 7.20 (d, 1H, $J = 8.8$), 7.35 (s, 1H). ^{13}C NMR ($CDCl_3$): 20.6, 21.3, 22.2, 27.0, 29.5, 32.9, 64.2, 73.6, 110.6, 113.2, 115.5, 120.8, 126.2, 142.2, 149.6, 150.5, 171.4.

2.5. 3-(2-Bromo-7,7-dimethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-1-yl)propyl acetate (**7**)

Compound **6** (0.11 g, 0.36 mmol) was dissolved in ethanol (20 mL) and *N*-bromosuccinimide (0.071 g, 0.4 mmol) was added. The solution was stirred for 40 min and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 6:1) to yield compound **6** as wax (0.12 g, 86%, traces of a bis-brominated product were observed). HRMS (ES) calc. for: $C_{18}H_{21}^{79}BrO_4$ 381.0702; found: 381.1157. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.88 (t, 2H, $J = 6.7$), 1.98 (m, 2H), 2.08 (s, 3H), 2.81 (m, 2H), 3.06 (t, 2H, $J = 6.7$), 4.18 (t, 2H, $J = 6.4$), 6.73 (d, 1H, $J = 8.9$), 7.17 (d, 1H, $J = 8.9$). ^{13}C NMR ($CDCl_3$): 20.2, 21.3, 22.4, 26.9, 30.0, 32.7, 64.0, 73.8, 110.3, 112.3, 115.4, 119.3, 126.6, 127.5, 150.2, 150.2, 171.4.

2.6. Preparation of compounds **8a**,**b**

In a 60 mL round-bottomed thick glass tube fitted with a PTFE-faced screw-cap, compound **7** (0.2 g, 5.26 mmol), pyridine-4-boronic acid (9.47 mmol) or pyridine-3-boronic acid 1,3-propanediol ester (9.47 mmol), cesium carbonate (0.68 g, 21 mmol) were dispersed in a water (2 mL)–dioxane (5 mL) mixture. This was degassed with slow stream of argon for 10 min before adding [1,1′-bis(diphenylphosphino)ferrocene] dichloropalladium (II) complexed with dichloromethane (0.02 g, 0.26 mmol). The tube was tightly closed and heated at 80 °C for 8 h. The resulting solution was dispersed in ethyl acetate, washed with water; the organic phase was dried over sodium sulfate and concentrated to dryness. The residue was purified by a chromatography over silica gel (cyclohexane/ethyl acetate 3:2) to yield compounds **8a**,**b** as described below.

2.6.1. 3-(7,7-Dimethyl-2-(pyridin-4-yl)-8,9-dihydro-7H-furo[3,2-f]chromen-1-yl)propyl acetate (**8a**)

Obtained in a 60% yield as a wax, which contained traces of a bis-brominated derivative of **7**. HRMS (ES) calc. for: $C_{23}H_{26}NO_4$ 380.1862; found: 380.1868. ^{1}H NMR ($CDCl_3$): 1.39 (s, 6H), 1.91 (t, 2H, $J = 6.7$), 2.09 (s, 3H), 2.10 (m, 2H), 3.14 (m, 4H), 4.23 (t, 2H, $J = 6.1$), 6.85 (d, 1H, $J = 8.9$), 7.26 (d, 1H, $J = 8.9$), 7.68 (m, 2H), 8.71 (m, 2H). ^{13}C NMR ($CDCl_3$): 19.9, 20.8, 21.9, 26.5, 30.3, 32.4, 63.6, 73.3, 110.3, 113.0, 117.3, 120.4, 120.7, 127.2, 138.8, 148.1, 149.7, 148.8, 170.8.

2.6.2. 3-(7,7-Dimethyl-2-(pyridin-3-yl)-8,9-dihydro-7H-furo[3,2-f]chromen-1-yl)propyl acetate (**8b**)

Obtained in a 55% yield as a wax. HRMS (ES) calc. for: $C_{23}H_{26}NO_4$ 380.1862; found: 380.1884. ^{1}H NMR ($CDCl_3$): 1.39 (s, 6H), 1.91 (t, 2H, $J = 6.7$), 2.07 (s, 3H), 2.08 (m, 2H), 3.08 (m, 2H), 3.17 (t, 2H, $J = 6.7$), 4.19 (t, 2H, $J = 6.1$), 6.82 (d, 1H, $J = 8.8$), 7.26 (d, 1H, $J = 8.8$), 7.44 (m, 1H), 8.06 (m, 1H), 8.62 (m, 1H), 9.00 (m, 1H). ^{13}C NMR ($CDCl_3$): 19.9, 20.8, 21.7, 26.6, 30.7, 32.5, 63.5, 73.3, 110.2, 112.9, 116.3, 118.2, 123.7, 127.2, 127.8, 134.5, 147.4, 148.3, 148.5, 149.1, 149.7, 170.9.

2.7. Preparation of compounds **9a**,**b**

Esters **8a**,**b** (0.15 g, 0.39 mmol) were dissolved in 1 N sodium methanolate in methanol solution (10 mL) and stirred overnight. The solution was partially concentrated, dispersed in dichloromethane and the organic phase was washed with water; the organic phase was dried over sodium sulfate and concentrated to dryness to yield pure compounds **9a**,**b** as described below. Nota NMR measurement had to be made in DMSO-d_6 as in $CDCl_3$, the occurrence of two unequal sets of signals was observed.

2.7.1. 3-(7,7-Dimethyl-2-(pyridin-4-yl)-8,9-dihydro-7H-furo[3,2-f]chromen-1-yl)propan-1-ol (**9a**)

Obtained in a 45% yield as solid after a recrystallisation in a toluene/cyclohexane mixture. m.p. = 142 °C. HRMS (ES) calc. for: $C_{21}H_{24}NO_3$ 338.1756; found: 338.1731. ^{1}H NMR (DMSO-d_6): 1.30 (s, 6H), 1.86 (m, 4H), 3.06 (m, 2H), 3.14 (m, 2H), 3.59 (m, 2H), 4.68 (t (ex), 1H, $J = 5.1$), 6.78 (d, 1H, $J = 8.8$), 7.32 (d, 1H, $J = 8.8$), 7.72 (m, 2H), 8.68 (m, 2H). ^{13}C NMR (DMSO-d_6): 20.0, 22.1, 27.1, 32.6, 35.0, 61.1, 74.0, 110.9, 114.5, 117.5, 120.8, 122.6, 128.0, 138.3, 148.2, 149.1, 150.1, 151.1.

2.7.2. 3-(7,7-Dimethyl-2-(pyridin-3-yl)-8,9-dihydro-7H-furo[3,2-f]chromen-1-yl)propan-1-ol (**9b**)

Obtained in a 95% yield as a solid. m.p. = 65 °C. HRMS (ES) calc. for: $C_{21}H_{24}NO_3$ 338.1756; found: 338.1764. ^{1}H NMR (DMSO-d_6): 1.30 (s, 6H), 1.86 (m, 4H), 2.99 (m, 2H), 3.16 (t, 2H, $J = 6.7$), 3.55 (m, 2H), 4.63 (t (ex), 1H, $J = 5.1$), 6.73 (d, 1H, $J = 8.8$), 7.31 (d, 1H, $J = 8.8$), 7.55 (m, 1H), 8.12 (m, 1H), 8.60 (m, 1H), 8.95 (m, 1H). ^{13}C NMR (DMSO-d_6): 19.6, 21.6, 26.8, 32.3, 35.1, 60.7, 73.6, 110.3, 113.8, 116.1, 119.7, 124.4, 127.6, 134.3, 147.6, 148.3, 148.7, 149.3, 149.7.

2.8. ((6-Hydroxy-2,2,7,8-tetramethylchroman-5-yl)methyl) triphenylphosphonium bromide (**11**)

A solution of this compound was prepared by reacting compound **10** (4.6 g, 15.41 mmol; first prepared as previously described [10]) and triphenylphosphine (4.05 g, 15.47 mmol) in dichloromethane (9.2 mL, dried over 4 Å molecular sieves). LC/MS monitoring of this solution pointed out its stability over time and this was thus used as a stock solution for the preparation of some of the compound below.

Further investigations led to the following procedure which allows the isolation of this phosphonium salt. To a solution of 2,2,5,7,8-pentamethylchroman-6-ol (10.66 g, 0.048 mol) in toluene (300 mL), *N*-bromosuccinimide (8.61 g, 0.048 mol) was added. The solution was stirred for 45 min and triphenylphosphine (12.94 g, 0.049 mol) was added. This was stirred overnight, the resulting suspension was heated to reflux, filtered while hot and the precipitate was further washed with boiling toluene (200 mL). The resulting white powder was dried under vacuum at 60 °C to yield pure compound **11** (23.3 g, 85%). m.p. > 260 °C. HRMS (ES) calc. for: $C_{32}H_{34}PO_2$ 481.2296; found: 481.2310. ^{1}H NMR ($CDCl_3$): 1.09 (s, 6H), 1.45 (t, 2H, $J = 6.7$), 1.97 (s, 3H), 2.01 (d, 3H, $J = 3.0$), 2.16 (t, 2H, $J = 6.7$), 5.99 (d, 2H, $J = 13.1$), 7.58 (m, 12H), 7.71 (m, 3H). ^{13}C NMR ($CDCl_3$): 12.2, 13.3, 21.6, 25.8 (d, $J = 46$), 26.5, 32.8, 72.5, 112.6 (d, $J = 9$), 116.2 (d, $J = 5$), 119.0 (d, $J = 84$), 125.3, 126.6 (d, $J = 5$), 129.8 (d, $J = 12$), 134.2 (d, $J = 10$), 134.6 (d, $J = 3$), 146.2 (d, $J = 3$), 146.9.

2.9. 3-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)pyridine (**13a**)

A solution of **10** (0.25 g, 0.83 mmol) and triphenylphosphine (0.22 g, 0.84 mmol) was stirred in cyclohexane (20 mL; dried over 4 Å molecular sieves) for 2 h. The solvent was removed under vacuum at room temperature before nicotinoyl chloride hydrochloride (0.16 g, 0.90 mmol), triethylamine (0.38 mL, 2.7 mmol) and toluene (20 mL; dried over 4 Å molecular sieves) were added. The mixture was then heated at 115 °C for 12 h. Upon cooling, volatiles were removed via rotary evaporation, and the residue was purified by a chromatography over silica gel (ethyl acetate/cyclohexane 1:2). Further purification of the corresponding chromatographic fraction was achieved by a second chromatography over neutral alumina containing 1.5% water (ethyl acetate/cyclohexane 1:6) to give compound **13a** as a solid (0.097 g, 38% yield). m.p. = 142 °C. HRMS (ES) calc. for: $C_{20}H_{22}NO_2$ 308.1651; found: 308.1709. ^{1}H NMR ($CDCl_3$): 1.38 (s, 6H), 1.90 (t, 2H, J = 6.8), 2.24 (s, 3H), 2.49 (s, 3H), 2.92 (t, 2H, J = 6.8), 7.05 (s, 1H), 7.40 (dd, 1H, J = 4.7, 8.0), 8.15 (td, 1H, J = 1.7, 8.0), 8.55 (d, 1H, J = 4.7), 9.11 (d, 1H, J = 1.7). ^{13}C NMR ($CDCl_3$): 12.3, 12.4, 20.5, 27.2, 32.7, 74.1, 101.9, 109.1, 118.8, 123.9, 124.1, 125.0, 127.9, 132.2, 145.9, 148.30, 148.33, 149.2, 151.7.

2.10. Preparation of compounds **13b–e** from acyl chlorides

In a 40 mL round-bottomed thick glass tube fitted with a PTFE-faced cap, the stock dichloromethane solution of the phosphonium salt **11** (1.67 mmol) described above, the relevant acyl chloride (2.1 mmol) and triethylamine (0.95 mL, 4.8 mmol, dried over 4 Å molecular sieves) were mixed in dichloromethane (10 mL, dried over 4 Å molecular sieves). This was refluxed for 88 h and then concentrated to dryness. The resulting residues containing compounds **13b–d** were purified accordingly as described below.

2.10.1. (4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)methyl acetate (**13b**)

This compound was obtained as a solid in a 80% yield after a chromatography over silica gel (ethyl acetate/cyclohexane 1:9). m.p. = 93 °C. HRMS (ES) calc. for: $C_{18}H_{22}O_4Na$ 325.1416; found: 325.1432. ^{1}H NMR ($CDCl_3$): 1.39 (s, 6H), 1.87 (t, 2H, J = 6.8), 2.15 (s, 3H), 2.25 (s, 3H), 2.45 (s, 3H), 2.87 (t, 2H, J = 6.8), 5.22 (s, 2H), 6.71 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.2, 12.5, 20.5, 21.3, 27.2, 32.9, 59.3, 74.1, 106.3, 109.2, 118.8, 123.4, 124.1, 148.0, 149.2, 151.0, 171.0.

2.10.2. 4-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)pyridine (**13c**)

This compound was obtained as a solid in a 80% yield after a chromatography over silica gel (ethyl acetate/cyclohexane 1:1). m.p. = 159 °C. HRMS (ES) calc. for: $C_{20}H_{22}NO_2$ 308.1651; found: 308.1637. ^{1}H NMR ($CDCl_3$): 1.38 (s, 6H), 1.89 (t, 2H, J = 6.8), 2.25 (s, 3H), 2.48 (s, 3H), 2.91 (t, 2H, J = 6.8), 7.15 (s, 1H), 7.68 (m, 2H), 8.66 (m, 2H). ^{13}C NMR ($CDCl_3$): 12.3, 12.4, 20.5, 27.2, 32.7, 74.1, 104.0, 109.2, 118.8, 118.9, 124.8, 124.9, 138.5, 148.4, 149.4, 150.4, 151.9.

2.10.3. 2-Chloro-5-(4,5,7,7-tetramethyl-8,9-dihydro-7H-furo-[3,2-f]chromen-2-yl)pyridine (**13d**)

This compound was obtained as a solid in a 90% yield after a chromatography over silica gel (dichloromethane/cyclohexane 3:1). m.p. = 140 °C. HRMS (ES) calc. for: $C_{20}H_{21}^{35}ClNO_3$ 342.1261; found: 342.1284. ^{1}H NMR ($CDCl_3$): 1.38 (s, 6H), 1.88 (t, 2H, J = 6.8), 2.24 (s, 3H), 2.46 (s, 3H), 2.89 (t, 2H, J = 6.8), 7.00 (s, 1H), 7.36 (dd, 1H, J = 0.4 and 8.3), 8.04 (dd, 1H, J = 2.5 and 8.3), 8.83 (d, 1H, J = 2.5). ^{13}C NMR ($CDCl_3$): 12.3, 12.5, 20.5, 27.2, 32.7, 74.1, 102.2, 109.1, 118.7, 124.1, 124.6, 124.9, 126.6, 134.4, 146.0, 148.4, 149.1, 150.3, 150.7.

2.10.4. 2-(4-Chlorobenzyl)-4,5,7,7-tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromene (**13e**)

This compound was obtained as a solid in a 50% yield after a chromatography over silica gel (dichloromethane/cyclohexane 3:97). m.p. = 78 °C. HRMS (ES) calc. for: $C_{22}H_{23}^{35}ClO_2$ 355.1465; found: 355.1355. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.85 (t, 2H, J = 6.8), 2.22 (s, 3H), 2.40 (s, 3H), 2.82 (t, 2H, J = 6.8), 4.08 (s, 2H), 6.27 (s, 1H), 7.25 (m, 2H), 7.32 (m, 2H). ^{13}C NMR ($CDCl_3$): 11.7, 12.1, 20.2, 26.8, 32.5, 34.5, 73.5, 101.9, 108.4, 118.0, 121.3, 124.3, 128.6, 130.3, 132.4, 136.3, 147.4, 148.3, 155.8.

2.11. Preparation of compounds **13f–g** from carboxylic acids and dicyclohexylcarbodiimide

In a 40 mL round-bottomed thick glass tube fitted with a PTFE-faced cap, the relevant acid (1.75 mmol) and dicyclohexylcarbodiimide (1.77 mmol) were dissolved in dichloromethane (5 mL, dried over 4 Å molecular sieves). After stirring for 30 min, the stock dichloromethane solution of the phosphonium salt **11** (1.67 mmol) described above was added. After another 30 min of stirring, triethylamine (0.95 mL, 4.8 mmol, dried over 4 Å molecular sieves) was added and this was refluxed for 88 h before concentrating it to dryness. The resulting paste was dispersed in boiling cyclohexane, filtered and the filtrate concentrated to dryness. The resulting residue was purified as described below.

2.11.1. 2-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)acetonitrile (**13f**)

This compound was obtained as a solid in a 5.5% yield after a chromatography over silica gel (ethyl acetate/cyclohexane 1:6). m.p. = 143 °C. HRMS (ES) calc. for: $C_{17}H_{20}NO_2$ 270.1494; found: 270.1487. ^{1}H NMR ($CDCl_3$): 1.36 (s, 6H), 1.86 (t, 2H, J = 6.8), 2.21 (s, 3H), 2.39 (s, 3H), 2.85 (t, 2H, J = 6.8), 3.91 (s, 2H), 6.65 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.2, 12.4, 18.6, 20.5, 27.2, 32.7, 74.0, 104.2, 109.1, 115.9, 118.6, 123.2, 124.0, 144.9, 148.2, 149.2.

2.11.2. 2-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)pyridine (**13g**)

This compound was obtained as a solid in a 80% yield after a chromatography over silica gel (ethyl acetate/cyclohexane 1:9). m.p. = 126 °C. HRMS (ES) calc. for: $C_{20}H_{22}NO_2$ 308.1651; found: 308.1666. ^{1}H NMR ($CDCl_3$): 1.39 (s, 6H), 1.89 (t, 2H, J = 6.8), 2.26 (s, 3H), 2.51 (s, 3H), 2.93 (t, 2H, J = 6.8), 7.20 (m, 1H), 7.44 (s, 1H), 7.76 (m, 1H), 7.92 (d, 1H, J = 7.9), 8.66 (d, 1H, J = 4.6). ^{13}C NMR ($CDCl_3$): 12.3, 12.5, 20.4, 27.2, 32.8, 74.1, 104.0, 109.5, 118.7, 119.7, 122.6, 124.1, 125.2, 137.1, 148.3, 149.4, 150.0, 150.2, 154.3.

2.11.3. 3-((4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)methyl)pyridine (**13h**)

This compound was obtained as a solid in a 27% yield after two successive chromatographies over silica gel (ethyl acetate/cyclohexane 1:2 and then ethyl acetate/dichloromethane 1:6). m.p. = 89 °C. HRMS (ES) calc. for: $C_{21}H_{24}NO_2$ 322.1807; found: 322.1846. ^{1}H NMR ($CDCl_3$): 1.35 (s, 6H), 1.84 (t, 2H, J = 6.8), 2.21 (s, 3H), 2.39 (s, 3H), 2.81 (t, 2H, J = 6.8), 4.11 (s, 2H), 6.29 (s, 1H), 7.27 (m, 1H), 7.64 (m, 1H), 8.54 (m, 1H), 8.63 (m, 1H). ^{13}C NMR ($CDCl_3$): 12.1, 12.5, 20.5, 27.2, 32.8, 32.82, 74.8, 102.5, 108.8, 118.4, 121.9, 123.9, 124.6, 133.8, 136.8, 147.8, 148.4, 148.8, 150.5, 155.4.

2.12. Preparation of compounds **13i,j** from carboxylic acids and oxalyl chloride

In a 40 mL round-bottomed thick glass tube fitted with a PTFE-faced cap, the relevant acid (2.08 mmol), oxalyl chloride (1.2 mL, 2.40 mmol) and a drop of dimethylformamide were stirred in

dichloromethane (10 mL, dried over 4 Å molecular sieves) for 10 h. The stock dichloromethane solution of the phosphonium salt **11** (1.67 mmol) described above was then added followed by triethylamine (1.2 mL, 8.4 mmol; dried over 4 Å molecular sieves). This was refluxed for 64 h before concentrating it to dryness. The resulting residues containing compounds **13i,j** were purified accordingly as described below.

*2.12.1. 2-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)pyrazine (**13i**)*

This compound was obtained as a solid in a 52% yield after a chromatography over silica gel (ethyl acetate/cyclohexane 1:3). m.p. = 140 °C. HRMS (ES) calc. for: $C_{19}H_{21}N_2O_2$ 309.1603; found: 309.1587. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.87 (t, 2H, J = 6.8), 2.24 (s, 3H), 2.48 (s, 3H), 2.90 (t, 2H, J = 6.8), 7.44 (s, 1H), 8.44 (d, 1H, J = 2.4), 8.55 (dd, 1H, J = 1.1 and 2.4), 9.13 (d, 1H, J = 1.1). ^{13}C NMR ($CDCl_3$): 12.4, 12.5, 20.4, 27.2, 32.7, 74.1, 106.0, 109.5, 118.9, 124.8, 125.1, 141.4, 143.1, 144.5, 145.9, 148.5, 149.8, 151.8.

*2.12.2. 4,5,7,7-Tetramethyl-2-(tetrahydrofuran-2-yl)-8,9-dihydro-7H-furo[3,2-f]chromene (**13j**)*

This compound was obtained as a solid in a 60% yield after a chromatography over silica gel (dichloromethane/cyclohexane 2:1). m.p. = 98 °C. HRMS (ES) calc. for: $C_{19}H_{25}O_3$ 301.1804; found: 301.1818. ^{1}H NMR ($CDCl_3$): 1.36 (s, 6H), 2.04 (t, 2H, J = 6.7), 2.12 (m, 2H), 2.19 (s, 3H), 2.23 (m, 2H), 2.29 (s, 3H), 2.85 (t, 2H, J = 6.7), 3.95 (m, 1H), 4.08 (m, 1H), 5.08 (t, 1H, J = 6.3), 6.54 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.1, 12.5, 20.5, 26.3, 27.2, 31.1, 32.9, 68.9, 73.8, 75.0, 101.6, 109.6, 118.6, 122.2, 124.2, 147.8, 148.9, 157.4.

*2.13. Preparation of compounds **14a–c** from succinic amides*

In a 40 mL round-bottomed thick glass tube fitted with a PTFE-faced cap, succinic anhydride (0.18 g, 1.87 mmol) and the relevant secondary amine (1.86 mmol) in dichloromethane (5 mL, dried over 4 Å molecular sieves) were refluxed for 1 h. Upon cooling, dicyclohexylcarbodiimide (0.39 g, 1.89 mmol) was added and the solution was stirred for 30 min at room temperature prior to the addition of the stock dichloromethane solution of the phosphonium salt **11** (1.67 mmol) described above and triethylamine (0.95 mL, 6.8 mmol, dried over 4 Å molecular sieves). This was heated at 65 °C for 88 h and then concentrated to dryness. The resulting paste was dispersed in boiling cyclohexane, filtrated and the filtrate was concentrated to dryness prior to a purification as described below.

*2.13.1. 4-[3-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)propanoyl]morpholine (**14a**)*

This compound was obtained as a solid in a 22% yield after two successive chromatographies over silica gel (dichloromethane/ethanol 95:5 and then ethyl acetate/cyclohexane 1:3). m.p. = 120 °C. HRMS (ES) calc. for: $C_{22}H_{30}NO_4$ 372.2175; found: 372.2163. ^{1}H NMR ($CDCl_3$): 1.35 (s, 6H), 1.84 (t, 2H, J = 6.8), 2.20 (s, 3H), 2.39 (s, 3H), 2.76 (t, 2H, J = 6.7), 2.82 (m, 2H), 3.14 (m, 2H), 3.47 (m, 2H), 3.61 (m, 2H), 3.66 (m, 4H), 6.35 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.1, 12.5, 20.6, 24.8, 27.2, 31.8, 32.8, 42.4, 46.3, 67.0, 67.3, 73.8, 101.4, 108.7, 118.1, 121.5, 124.8, 147.8, 148.4, 156.8, 170.7.

*2.13.2. 4-[3-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)propanoyl] 1-methylpiperazine (**14b**)*

This compound was obtained as a solid in a 39% yield after a chromatography over silica gel (dichloromethane/2 N ethanolic ammonia 95:5). m.p. = 86 °C. HRMS (ES) calc. for: $C_{23}H_{33}N_2O_3$ 385.2491; found: 385.2502. ^{1}H NMR ($CDCl_3$): 1.34 (s, 6H), 1.84 (t, 2H, J = 6.8), 2.29 (s, 3H), 2.34 (s, 3H), 2.38 (m, 2H), 2.40 (s, 3H), 2.77 (m, 2H), 2.82 (t, 2H, J = 6.8), 3.13 (t, 2H, J = 7.0), 3.50 (m, 2H), 3.68 (m, 2H), 6.34 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.0, 12.5, 20.5, 24.9, 27.2, 31.9, 32.9, 41.9, 45.7, 46.3, 55.1, 55.4, 73.8, 101.3, 108.7, 118.2, 121.4, 124.8, 147.7, 148.4, 157.0, 170.5.

*2.13.3. 1-[3-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)propanoyl]pyrrolidine (**14c**)*

This compound was obtained as a solid in a 6% yield after a chromatography over silica gel (dichloromethane/ethanol 95:5). m.p. = 115 °C. HRMS (ES) calc. for: $C_{22}H_{30}NO_3$ 356.2226; found: 356.2205. ^{1}H NMR ($CDCl_3$): 1.35 (s, 6H), 1.89 (m, 4H), 1.93 (m, 2H), 2.20 (s, 3H), 2.39 (s, 3H), 2.71 (m, 2H), 2.82 (m, 2H), 3.15 (m, 2H), 3.42 (t, 2H, J = 7.4), 3.50 (t, 2H, J = 6.7), 6.34 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.0, 12.5, 20.6, 24.5, 24.8, 26.5, 27.2, 32.9, 33.5, 73.8, 101.1, 108.7, 118.2, 121.3, 124.9, 147.7, 148.4, 157.3, 170.6.

*2.14. Preparation of compounds **15a–c** using microwave heating*

In a typical procedure, in a 20 mL Biotage vial, the phosphonium salt **11** (1.96 g, 3.5 mmol), the corresponding acid (3.5 mmol), DCC (0.72 g, 3.5 mmol) and hydroxybenzotriazole (0.47 g, 3.5 mmol) were mixed in acetonitrile (dried over 4 Å molecular sieves, 14 mL). Triethylamine (2.45 mL, 17.4 mmol) was then added, the vial was sealed and submitted to the microwave heating (120 °C for 1 h, the absorbance of the medium being set to high). The resulting suspension was concentrated to dryness, dispersed in boiling cyclohexane, filtered and the filtrate was concentrated to dryness again. The resulting residue was purified as described below to provide compounds **15a–c**.

*2.14.1. (E)-3-(2-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo-[3,2-f]chromen-2-yl)vinyl)pyridine (**15a**)*

This compound was obtained as a solid in a 22% yield after a chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 95:5–3:1). m.p. = 149 °C. HRMS (ES) calc. for: $C_{22}H_{24}NO_2$ 334.1807; found: 334.1810. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.87 (t, 2H, J = 6.7), 2.24 (s, 3H), 2.48 (s, 3H), 2.87 (t, 2H, J = 6.7), 6.67 (s, 1H), 7.06 (d, 1H, J = 16.2), 7.23 (d, 1H, J = 16.2), 7.30 (m, 1H), 7.84 (m, 1H), 8.50 (m, 1H), 8.77 (d, 1H, J = 2.1). ^{13}C NMR ($CDCl_3$): 11.9, 12.1, 20.1, 26.8, 32.3, 73.6, 105.1, 108.7, 118.1, 118.9, 120.0, 123.5, 123.6, 124.5, 124.8, 132.5, 132.7, 147.7, 148.5, 148.6, 153.3.

*2.14.2. 3-(2-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)ethyl)pyridine (**15b**)*

This compound was obtained as an oil in a 10% yield after a chromatography over neutral alumina containing 1.5% water (cyclohexane/ethyl acetate 9:1–5:1). HRMS (ES) calc. for: $C_{22}H_{26}NO_2$ 336.1964; found: 336.1961. ^{1}H NMR ($CDCl_3$): 1.35 (s, 6H), 1.84 (t, 2H, J = 7.2), 2.21 (s, 3H), 2.40 (s, 3H), 2.81 (t, 2H, J = 7.2), 3.09 (s, 4H), 6.27 (s, 1H), 7.21 (m, 1H), 7.50 (m, 1H), 8.48 (m, 1H), 8.52 (d, 1H, J = 1.9). ^{13}C NMR ($CDCl_3$): 11.7, 12.1, 20.2, 20.8, 30.1, 31.4, 32.5, 73.4, 101.1, 108.3, 117.9, 121.1, 123.3, 124.3, 135.9, 136.4, 147.3, 147.7, 148.0, 150.0, 156.2.

*2.14.3. 4,5,7,7-Tetramethyl-2-(thiophen-2-yl)-8,9-dihydro-7H-furo[3,2-f]chromene (**15c**)*

This compound was obtained as a solid in a 26% yield after a chromatography over neutral alumina containing 1.5% water (cyclohexane/dichloromethane 95:5). m.p. = 102 °C. HRMS (ES) calc. for: $C_{19}H_{20}O_2S$ 313.1262; found: 313.1246. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.88 (t, 2H, J = 6.7), 2.20 (s, 3H), 2.46 (s, 3H), 2.89 (t, 2H, J = 6.7), 6.79 (s, 1H), 7.10 (q, 1H, J = 3.6 and 5.0), 7.31 (q, 1H, J = 1.0 and 5.0), 7.45 (q, 1H, J = 1.0 and 3.6). ^{13}C NMR ($CDCl_3$): 11.8, 12.1,

20.1, 26.8, 32.4, 73.6, 99.8, 108.5, 118.1, 122.5, 123.5, 123.6, 124.3, 124.9, 127.7, 134.2, 147.7, 148.0, 150.1.

2.14.4. 4,5,7,7-Tetramethyl-2-(thiophen-2-ylmethyl)-8,9-dihydro-7H-furo[3,2-f]chromene (**15d**)

This compound was also obtained using the microwave heating described above, although from the corresponding commercially available acyl chloride, as a low melting solid in a 33% yield after a chromatography over neutral alumina containing 1.5% water (cyclohexane/dichloromethane 95:5). HRMS (ES) calc. for: $C_{20}H_{22}O_2S$ 327.1419; found: 327.1439. ^{1}H NMR ($CDCl_3$): 1.35 (s, 6H), 1.84 (t, 2H, $J = 6.7$), 2.20 (s, 3H), 2.40 (s, 2H), 2.82 (t, 2H, $J = 6.7$), 4.31 (s, 2H), 6.35 (s, 1H), 6.98 (m, 2H), 7.21 (m, 2H). ^{13}C NMR ($CDCl_3$): 11.6, 12.1, 20.1, 26.8, 29.4, 32.5, 73.4, 101.5, 108.4, 118.0, 121.3, 124.2, 124.3, 125.8, 126.8, 140.0, 147.4, 148.3, 155.4.

2.15. 4,5,7,7-Tetramethyl-2-(pyridin-3-yl)-7H-furo[3,2-f]chromen-9(8H)-one (**16**)

Compound **13a** (0.11 g, 0.36 mmol) was dissolved in a mixture of acetonitrile (10 mL), water (1 mL) and dichloromethane (4 mL). This was cooled to −42 °C and cerium ammonium nitrate (0.8 g, 1.46 mmol) dissolved in a water (2 mL)–acetonitrile (2 mL) mixture was added. The temperature was allowed to warm to room temperature for 1 h and the mixture was diluted in dichloromethane. The organic phase was washed with water and dried over magnesium sulfate. The residue obtained after concentration to dryness was purified by a chromatography over silica gel (dichloromethane/ethyl acetate 3:1) leading to compound **16** as a solid (0.085 g, 74%). m.p. = 182 °C. HRMS (ES) calc. for: $C_{20}H_{20}NO_3$ 322.1443; found: 322.1461. ^{1}H NMR ($CDCl_3$): 1.51 (s, 6H), 2.25 (s, 3H), 2.53 (s, 3H), 2.76 (s, 2H), 7.38 (m, 1H), 7.86 (s, 1H), 8.15 (m, 1H), 8.59 (m, 1H), 9.15 (m, 1H). ^{13}C NMR ($CDCl_3$): 12.2, 13.4, 27.1, 49.3, 79.6, 105.0, 110.2, 123.6, 123.7, 124.0, 127.2, 129.3, 132.3, 146.5, 149.4, 149.7, 154.7, 156.5, 193.5.

2.16. 3-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)pyridine 1-oxide (**17**)

Compound **13a** (0.2 g, 0.65 mmol) and 3-chloroperbenzoic acid (77%; 0.3 g, 1.30 mmol) were stirred overnight in dichloromethane (40 mL). The resulting solution was washed with a 1 N sodium hydroxide solution then with water and then dried over sodium sulfate. The residue obtained after concentration to dryness was further purified by a chromatography over silica gel (dichloromethane/ethanol 96:4) leading to compound **17** as a solid (0.11 g, 52%). m.p. = 176 °C. HRMS (ES) calc. for: $C_{20}H_{22}NO_3$ 324.1600; found: 324.1613. ^{1}H NMR ($CDCl_3$): 1.36 (s, 6H), 1.87 (t, 2H, $J = 6.8$), 2.23 (s, 3H), 2.43 (s, 3H), 2.89 (t, 2H, $J = 6.8$), 7.04 (s, 1H), 7.32 (m, 1H), 7.67 (m, 1H), 8.12 (m, 1H), 8.72 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.0 (two signals), 18.4, 20.1, 26.8, 32.2, 73.8, 103.6, 108.9, 118.5, 121.4, 124.2, 127.7, 125.9, 130.7, 135.2, 137.5, 148.2, 148.5, 149.0.

2.17. N1,N1-Dimethyl-N3-(5-(4,5,7,7-tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)pyridin-2-yl)propane-1,3-diamine (**18**)

Compound **13d** (0.10 g, 0.29 mmol) was heated to reflux under an inert atmosphere in *N*1,*N*1-dimethylpropane-1,3-diamine (4 mL) for 12 h. The resulting solution was concentrated to dryness using a high vacuum pump and the residue was purified by a chromatography over neutral alumina containing 1.5% water (dichloromethane/ethanol 98:2) leading to compound **18** as a wax (0.08 g, 63%). HRMS (ES) calc. for: $C_{25}H_{34}N_3O_2$ 408.2651; found: 408.2637. ^{1}H NMR ($CDCl_3$): 1.37 (s, 6H), 1.89 (m, 4H), 2.22 (s, 3H), 2.31 (s, 6H), 2.45 (s, 3H), 2.49 (t, 2H, $J = 6.7$), 2.89 (t, 2H, $J = 6.7$), 3.44 (m, 2H), 5.51 (m, 1H), 6.48 (dd, 1H, $J = 0.4$ and 8.6), 7.86 (dd, 1H, $J = 2.3$ and 8.1), 8.60 (m, 1H). ^{13}C NMR ($CDCl_3$): 11.7, 12.0, 20.2, 26.7, 26.8, 32.5, 41.2, 45.4, 58.0, 73.5, 97.2, 106.6, 108.2, 116.9, 118.0, 121.5, 125.1, 133.8, 145.1, 147.6, 147.9, 153.5, 158.3.

2.18. 5-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)pyridine-2-carbonitrile (**19**)

Compound **13d** (0.47 g, 1.38 mmol), zinc cyanide (0.1 g, 0.9 mmol), zinc (0.025 g, 0.38 mmol) and [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complexed with dichloromethane (0.005 g, 0.007 mmol) were mixed in dimethylacetamide (3 mL, dried over 4 Å molecular sieves). This was degassed by bubbling argon through the solution and then heated at 120 °C for 2 h. The cooled solution was diluted in dichloromethane, washed with water and brine and the organic phase dried over magnesium sulfate. After concentration to dryness, the residue was purified by chromatography over silica gel (dichloromethane) leading to compound **19** as a solid (0.46 g, 79%). m.p. = 194 °C. HRMS (ES) calc. for: $C_{21}H_{21}N_2O_2$ 333.1603; found: 333.1622. ^{1}H NMR ($CDCl_3$): 1.39 (s, 6H), 1.90 (t, 2H, $J = 6.8$), 2.25 (s, 3H), 2.47 (s, 3H), 2.91 (t, 2H, $J = 6.8$), 7.18 (s, 1H), 7.72 (dd, 1H, $J = 0.6$ and 8.1), 8.18 (dd, 1H, $J = 2.2$ and 8.1), 9.13 (dd, 1H, $J = 0.6$ and 2.2). ^{13}C NMR ($CDCl_3$): 12.1 (two signals), 20.5, 27.2, 32.6, 74.2, 104.8, 109.4, 117.8, 118.9, 124.8, 125.5, 128.8, 130.4, 131.6, 131.8, 147.3, 148.7, 149.7, 149.7, 149.8.

2.19. 5-(4,5,7,7-Tetramethyl-8,9-dihydro-7H-furo[3,2-f]chromen-2-yl)-2-(2H-tetrazol-5-yl)pyridine (**20**)

Compound **19** (0.15 g, 0.46 mmol), sodium azide (0.07 g, 1.08 mmol) and triethylamine hydrochloride (0.18 g, 1.31 mmol) were dispersed in toluene (12 mL). This was heated at 80 °C for 12 h and LC/MS monitoring pointed out the presence of large amount of starting material. Thus another amount of sodium azide (0.065 g, 1.0 mmol) and triethylamine hydrochloride (0.14 g, 1.02 mmol) was added and LC/MS monitoring was repeated after about every 10 h. Accordingly, the same quantity of sodium azide and triethylamine hydrochloride was repeatedly added until the completion of the reaction. This required the operation to be repeated four more times. After concentration to dryness, the residue was cautiously made acid with acetic acid (1 mL) and the resulting mixture was purified by a chromatography over silica gel (dichloromethane/ethanol/acetic acid 95:5:0.1) leading to compound **20** as a solid (0.15 g, 89%). m.p. > 260 °C. HRMS (ES) calc. for: $C_{21}H_{22}N_5O_2$ 376.1774; found: 376.1794. ^{1}H NMR ($CDCl_3$): 1.31 (s, 6H), 1.84 (t, 2H, $J = 6.8$), 2.14 (s, 3H), 2.43 (s, 3H), 2.88 (t, 2H, $J = 6.8$), 7.70 (s, 1H), 8.29 (d, 1H, $J = 8.2$), 8.47 (d, 1H, $J = 8.2$), 9.29 (s, 1H). ^{13}C NMR ($CDCl_3$): 12.7 (two signals), 20.4, 27.4, 32.4, 74.5, 105.0, 109.9, 118.6, 123.6, 124.0, 125.4, 128.9, 133.4, 143.2, 146.6, 148.4, 149.0, 151.1, 155.6.

2.20. Methyl 5-(4,5,7,7-tetramethyl-8,9-dihydro-7H-furo[3,2-f]-chromen-2-yl)pyridine-2-carboximidoate (**21**)

The nitrile-bearing compound **15** (0.44 g, 1.33 mmol) was dissolved in methanol (10 mL, dried over 4 Å molecular sieves) and potassium terbutanolate (0.18 g, 1.65 mmol) was added. This was stirred under an inert atmosphere at room temperature for three days. The resulting precipitate was then filtered and dried under vacuum to provide pure compound **21** as a solid (0.44 g, 92%). m.p. = 135 °C. HRMS (ES) calc. for: $C_{22}H_{24}N_2O_3$ 365.1865; found: 365.1884. ^{1}H NMR ($CDCl_3$): 1.38 (s, 6H), 1.89 (t, 2H, $J = 6.8$), 2.24 (s, 3H), 2.48 (s, 3H), 2.91 (t, 2H, $J = 6.8$), 4.08 (s, 3H), 7.10 (s, 1H), 7.89 (dd, 1H, $J = 0.5$ and 8.2), 8.17 (dd, 1H, $J = 2.2$ and 8.2), 9.10 (dd, 1H, $J = 0.5$ and 2.2), 9.21 (s (exch.), 1H). ^{13}C NMR ($CDCl_3$): 12.4

(two signals), 20.5, 21.2, 32.7, 54.3, 74.1, 103.0, 109.2, 118.8, 121.3, 124.4, 124.9, 129.0, 132.5, 145.7, 146.2, 148.4, 149.4, 151.2, 167.0.

Acknowledgement

We thank Gérard Gastine and Manon Vandervennet for their careful technical assistance in bacteriology. We thank Sanofi-Aventis as well as Pfizer for very generous donations of scientific equipment. This work received the financial support of the Institut Pasteur (GPH-5, DVPI) and the European Community (LHSP-CT-2005-018923).

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